A Dissertation on

"A STUDY ON NERVE CONDUCTION ABNORMALITIES IN PATIENTS WITH NEWLY DETECED THYROID DYSFUNCTION" AT GOVERNMENT STANLEY HOSPITAL, CHENNAI-600001.

Submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY CHENNAI – 600032.

In partial fulfillment of the Regulations for the
Award of the Degree of

M.D. BRANCH - I

GENERAL MEDICINE

DEPARTMENT OF GENERAL MEDICINE
STANLEY MEDICAL COLLEGE CHENNAI – 600 001

APRIL -2016

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This is to certify that **Dr. P.ARUNGANDHI,** Post - Graduate Student (JULY 2013 TO APRIL 2016) in the Department of General Medicine STANLEY MEDICAL COLLEGE, Chennai- 600001, has done this dissertation on "**A STUDY ON NERVE CONDUCTION ABNORMALITIES IN PATIENTS WITH NEWLY DETECED THYROID DYSFUNCTION"** under my guidance and supervision in partial fulfillment of the regulations laid down by the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D. (General Medicine), Degree Examination to be held in April 2016.

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DECLARATION

I **Dr.P.ARUNGANDHI** declare that I carried out this work "**A STUDY ON NERVE CONDUCTION ABNORMALITIES IN PATIENTS WITH NEWLY DETECED THYROID DYSFUNCTION"** at the Endocrinology OPD, and Medical OPD, Government Stanley Hospital during the period February 2015 to September 2015. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, or diploma to any other university, board either in India or abroad.

This is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulation for the M. D. Degree examination in General Medicine.

Dr.P.ARUNGANDHI

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At the outset I thank our Dean **Dr. ISAAC CHRISTIAN MOSES M.D,FICP,FACP** for permitting me to carry out this study in our hospital.

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Last but not the least; I sincerely thank all those **patients** who participated in this study, for their co-operation.

TABLE OF CONTENTS

ABBREVIATIONS

- T3 TRIIODOTHYRONINE
- T4 THYROXINE
- I IODIDE
- TPO THYROPEROXIDASE
- MIT MONOIODOTYROSINE
- DIT DIIODOTYROSINE
- RER ROUGH ENDOPLASMIC RETICULUM
- TSH THYROID STIMULATING HORMONE
- TRH THYROTROPIN RELEASING HORMONE
- EGF EPIDERMAL GROWTH FACTOR
- CGRP CALCITONIN GENE RELATED PEPTIDE
- AMP ADENOSINE MONOPHOSPHATE
- TSH-R Ab THYROID STIMULATING HORMONE RECEPTOR ANTIBODY
- FT4 FREE THYROXINE
- TBP THYROXINE BINDING PROTEIN
- FT4I FREE THYROXINE INDEX
- Tg THYROGLOBULIN
- EP PRE EJECTION PERIOD
- VET LEFT VENTRICULAR EJECTION TIME
- HBG STEROID HORMONE BINDING GLOBULIN
- CS NERVE CONDUCTION STUDY
- MAP COMPOUND MUSCLE ACTION POTENTIAL
- SNAP SENSORY NERVE ACTION POTENTIAL
- M MOTOR
- S SENSORY
- MNCV MOTOR NERVE CONDUCTION VELOCITY
- CTS CARPAL TUNNEL SYNDROME

INTRODUCTION

THYROID HISTORY:

The Chinese people in 1600 BC used seaweed and sponge which was burnt for the treatment of goitre. Pliny has given an account about the prevalence of an epidemic of goitre in Alps and mentions the use of burnt seaweed as treatment for it.

Galen in 150 AD also talks about the use of burnt sponge, spongia-usta, for the treatment of goitre. He suggested that lubricating the larynx was the major function of thyroid.

Wang Hei in 1475 described the anatomy of the thyroid gland and said that the remedy for goitre must be dried goitre. About fifty years later, Paracelsus said that goitre was due to the mineral impurities present in water. Thomas Wharton in1656 coined the name of the gland as THYROID meaning SHIELD.

Robert James Graves, doctor of Irish origin published a paper on exophthalmic goitre. Exophthalmic goitre is known as Basedow's disease in the European continent. Karl Adolph Basedow in 1840 had independently described this entity.

Only in the last century, the idea that thyroid produced an iodine containing substance was investigated, and Edward Calvin Kendall isolated thyroxine in 1914 as the active principle of thyroid gland.

REVIEW OF LITERATURE

The thyroid gland is the largest organ specialized for endocrine function in the human body. The major function of the thyroid follicular cells is to secrete a sufficient quantity of thyroid hormones, primarily tetraiodothyronine (T_4), and a lesser quantity of triiodothyronine (T_3). Thyroid hormones promote normal growth and development and regulate a number of homeostatic functions, including energy and heat production. In addition, the parafollicular cells of the human thyroid gland secrete calcitonin, which is important in calcium homeostasis.

THYROID GLAND

Embryology:

The morphogenesis of the thyroid gland, anterior-most organ which buds from gut tube, begins with thickening of endodermal epithelium in the foregut, referred to as thyroid anlage. The human thyroid anlage is first recognizable at embryonic day 16 or 17. This median thickening deepens and forms a small pit first and then an outpouching of the endoderm adjacent to the developing myocardial cells.[6]

The primitive stalk connecting the primordium with the pharyngeal floor elongates into the thyroglossal duct. During its caudal displacement, the primordium assumes a bilobate shape, coming into contact and fusing with the ventral aspect of the fourth pharyngeal pouch when it reaches its final position at about embryonic day 50.

The thyroglossal duct undergoes dissolution and fragmentation at the second month after conception, which leaves at the origin a small dimple at the junction of middle one-third and posterior one-thirds of the tongue called the foramen caecum. Cells of the lower portion of duct differentiate into thyroid, forming the pyramidal lobe of the gland. At the same time, the lobes contact the ultimobranchial glands, leading to conversion of C cells into the thyroid.

The histologic alterations occur in the entire gland. Complex, interconnecting, cord-like arrangements of cells mixed with vascular connective tissue replaces solid

epithelial mass and become tubule-like structures at third month of fetal life; shortly after that, follicular arrangements devoid of colloid appear, following which, at 13 to 14 weeks, the follicles starts to get filled with colloid.[4]

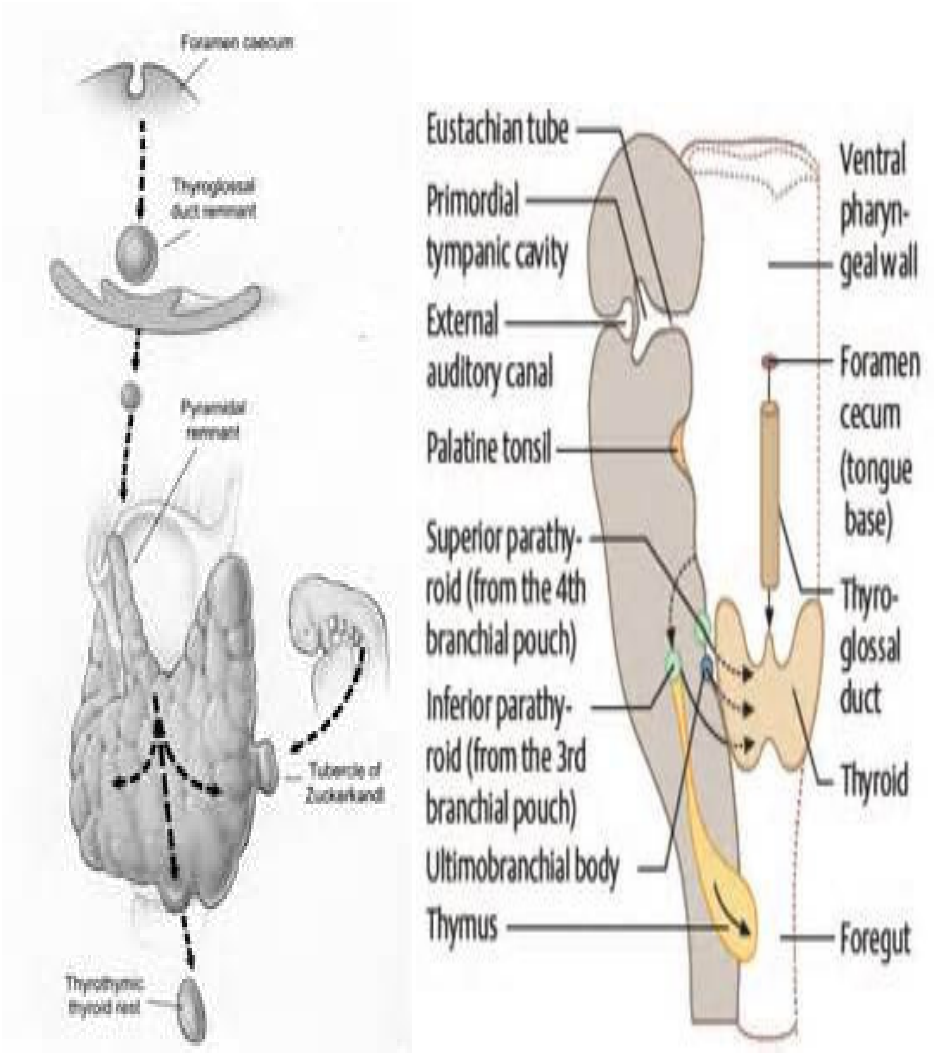


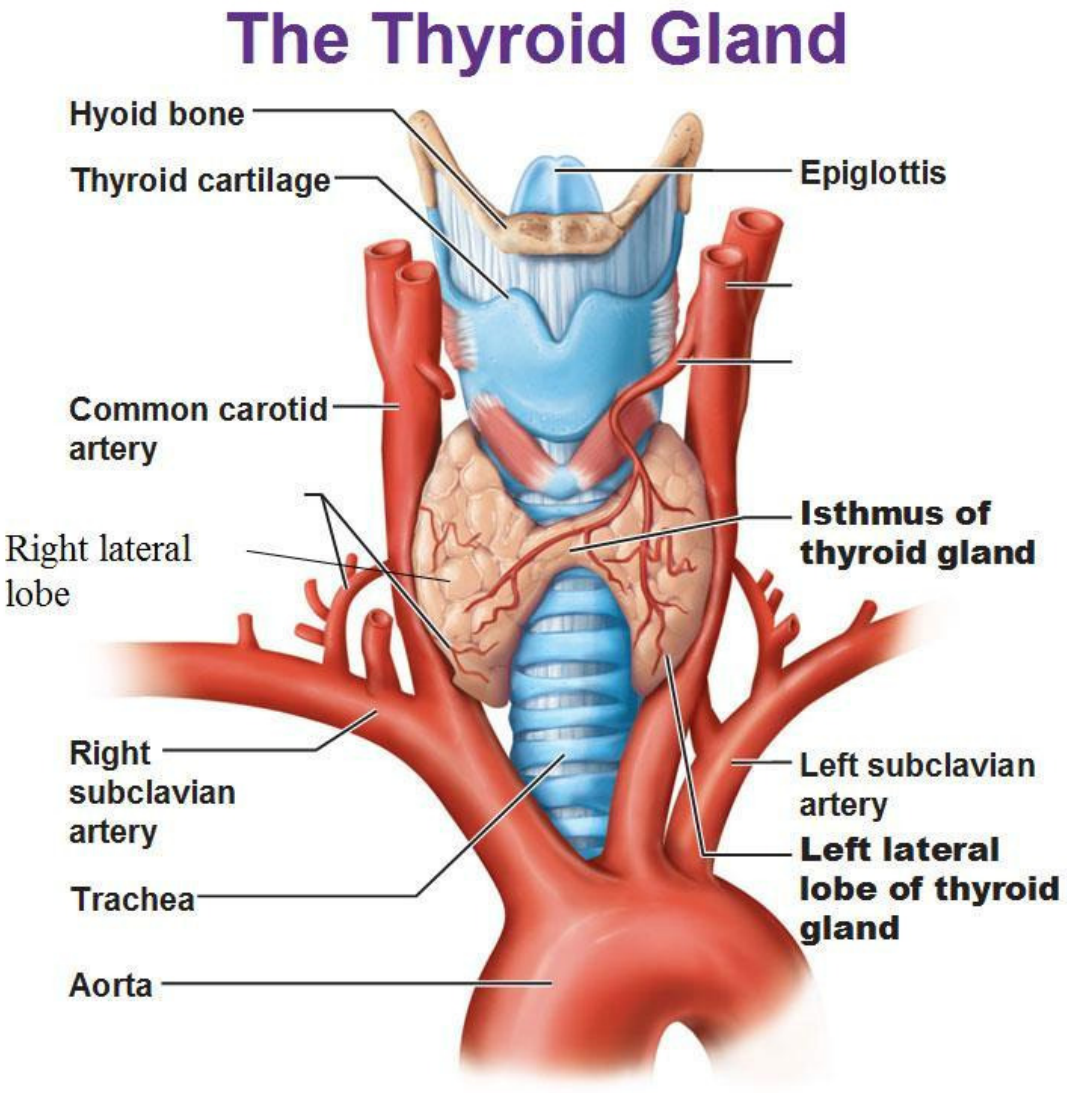
Fig: Evolution of Thyroid gland and its relation to the Branchial Arches

ANATOMY & HISTOLOGY

The thyroid gland originates from the floor of the pharynx, which elongates downward and anteriorly in relation to the trachea, divides into two lobes and forms a series of cellular cords[3]. Two lateral lobes are connected by a thin isthmus formed from those tiny balls or follicles. The origin of the gland at the base of the tongue is evident as the foramen cecum. The course of its downward migration is marked by the thyroglossal duct, remnants of which may persist in adult life as thyroglossal duct cysts. These are mucus-filled cysts, lined with squamous epithelium, and are usually found in the anterior neck between the thyroid cartilage and the base of the tongue. A remaining in the distal end of the thyroglossal duct is found in the pyramidal lobe, attached to the isthmus of the gland.

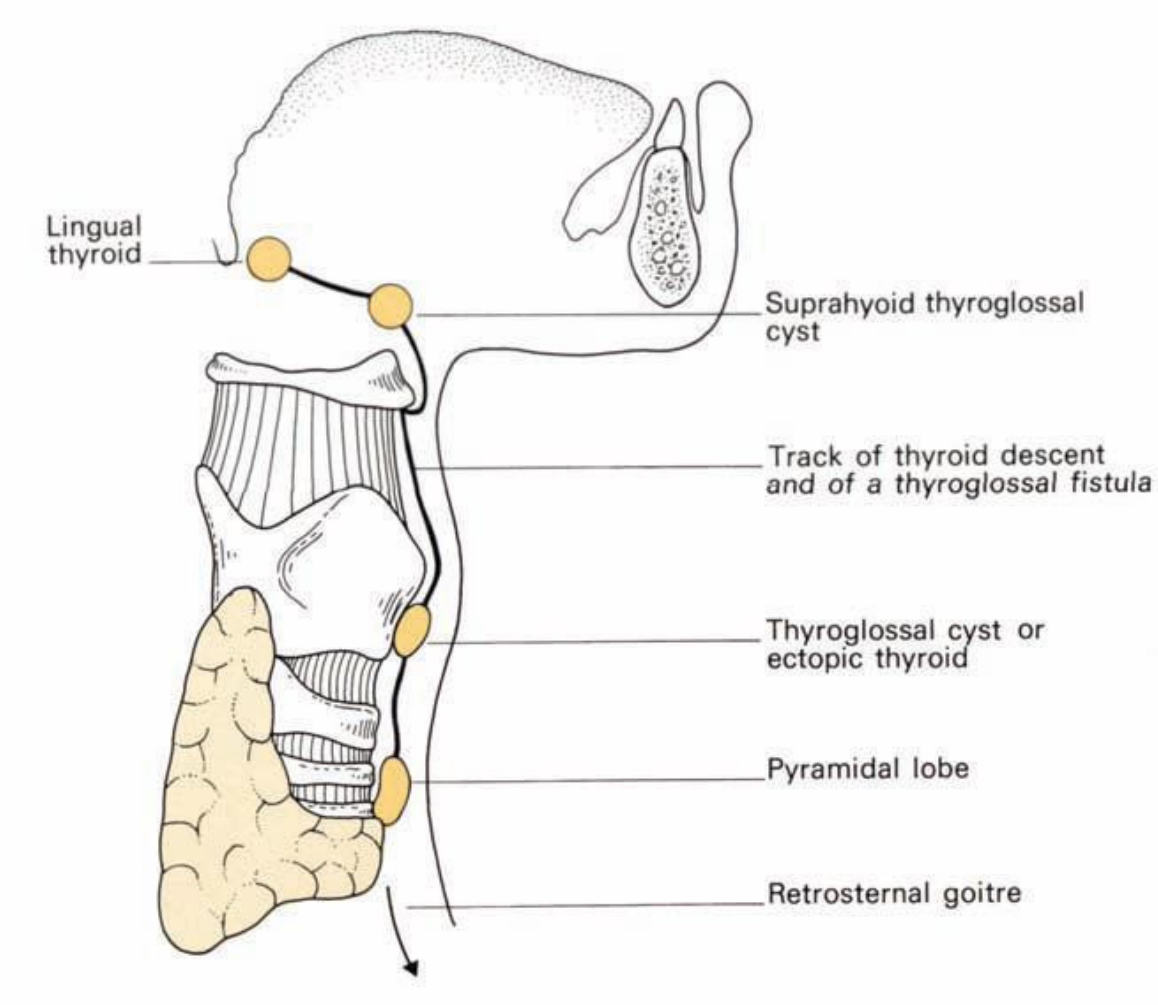
The isthmus of the thyroid gland is located just below the cricoid cartilage, midway between the apex of the thyroid cartilage ("Adam's apple") and the suprasternal notch. Each lobe is pear-shaped and measures about 2.5–4 ×1.5–2× 1–1.5 cms in dimension . The weight of the gland in the normal individual, as determined by ultrasonic examination, varies depending on dietary iodine intake, age, and body weight but in adults is approximately 10–20 g.

Sternothyroid muscle attachment prevents upward development of thyroid gland ; however,



Gross anatomy of the thyroid gland, anterior view

posterior and downward growth is unhampered, goiterous enlargement , will frequently extend posteriorly and inferiorly or even substernally.

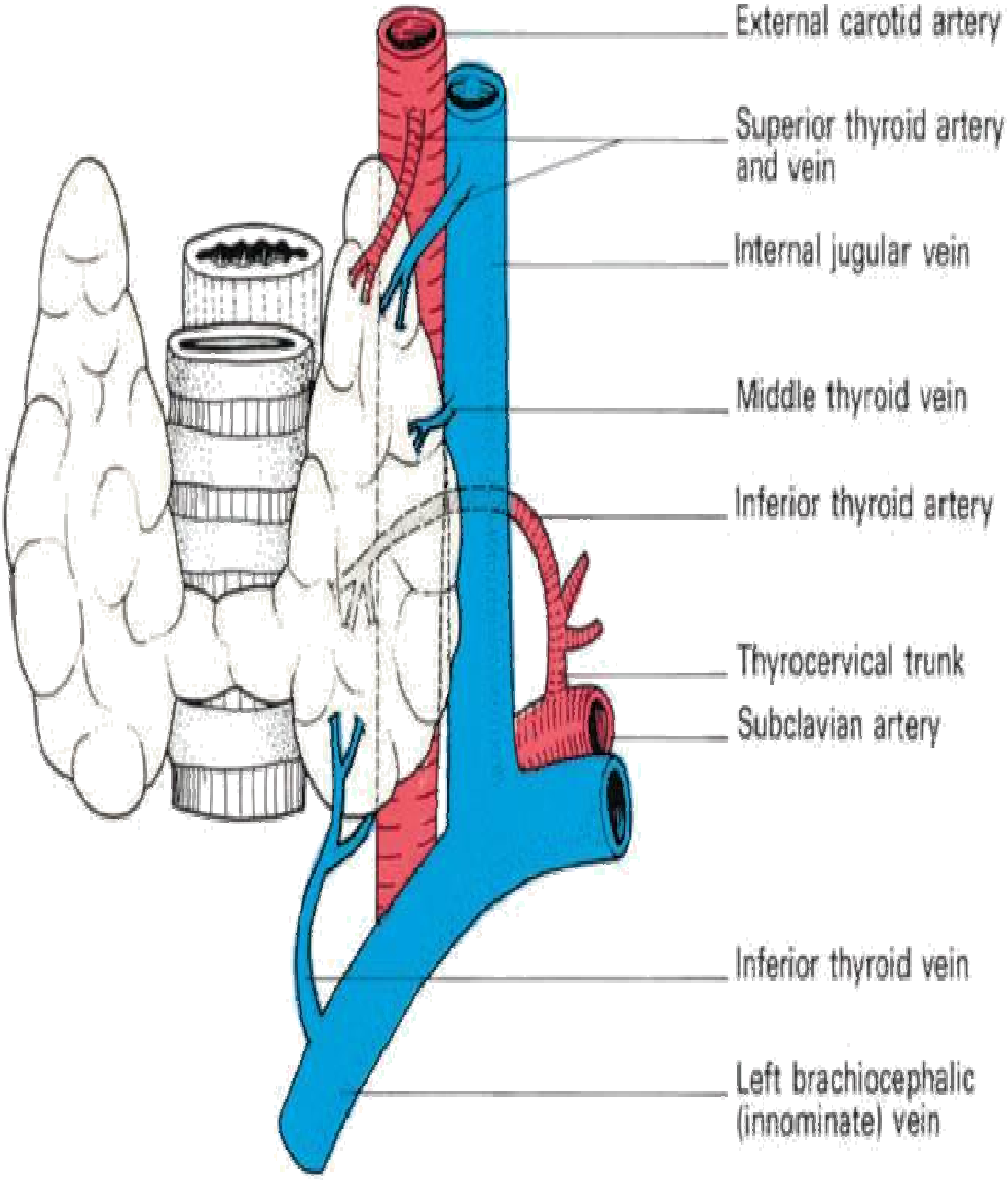


DEVELOPMENT OF THYROID GLAND

BLOOD SUPPLY OF THYROID

The thyroid gland is highly vascular organ . External carotid artery gives rise to superior thyroid artery , Thyrocervical trunk gives to inferior thyroid artery.and third and rare branch thyroid ima artery from brachiocephalic artery.

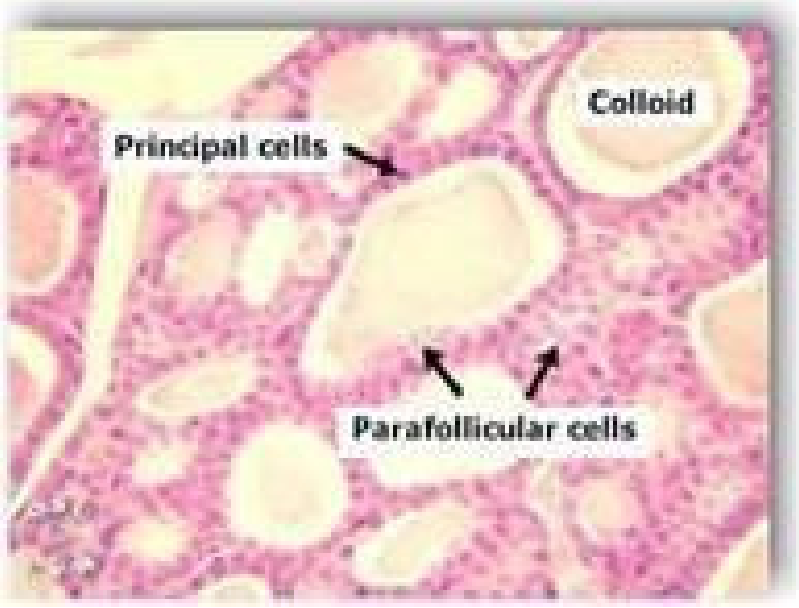
Superior, middle and inferior thyroid veins are formed from venous plexus on thyroid gland surface and on front of trachea. Superior and middle drains in internal jugular and inferior in innominate vein. In hyperthyroidism, the blood flow to the gland is markedly increased, and a whistling sound, or bruit, may be heard over the lower poles of the gland and may even be felt in the same areas as a vibration, or thrill. Other important anatomic considerations include the two pairs of parathyroid glands that usually lie behind the upper and middle thyroid lobes and the recurrent laryngeal nerves, which course along the trachea behind the thyroid gland.



BLOOD SUPPLY OF THYROID GLAND

HISTOLOGY

On microscopic examination, the thyroid gland is found to consist of a series of follicles of varying sizes. The follicles contain a pink-staining material (with hematoxylin-eosin stain) called “colloid” and is enclosed by thyroid epithelium. Tissue culture studies suggest that each follicle may represent an individual clone of cells. These cells become columnar when stimulated by TSH and flattened when resting . The follicle cells synthesize thyroglobulin, which is extruded into the lumen of the follicle. The biosynthesis of T_4 and T_3 occurs within thyroglobulin at the cell-colloid interface.Surface of follicle gives rise to many microvilli.; these are involved in endocytosis of thyroglobulin, which is then hydrolyzed in the cell to release thyroid hormones



HISTOLOGY OF THYROID GLAND

PHYSIOLOGY

STRUCTURE OF THYROID HORMONES

Hormones secreted by thyroid are very specialized in that they contain 59–65% of the trace element iodine. The iodinated thyronines are derived from iodination of the phenolic rings of tyrosine residues in thyroglobulin to form mono- or di iodotyrosine, which are coupled to form T_3 or T_4 .

IODINE METABOLISM

Iodine enters the body in food or water in the form of iodide or iodate ion, the iodate ion being converted to iodide in the stomach. In the course of millennia, iodine was extracted from the soil and washed down into the oceans, so that in mountainous and inland areas the supply of iodine may be quite limited, whereas the element is plentiful in coastal areas. The thyroid gland concentrates and traps iodide and synthesizes and stores thyroid hormones in thyroglobulin, which compensates for the scarcity of iodine[21].

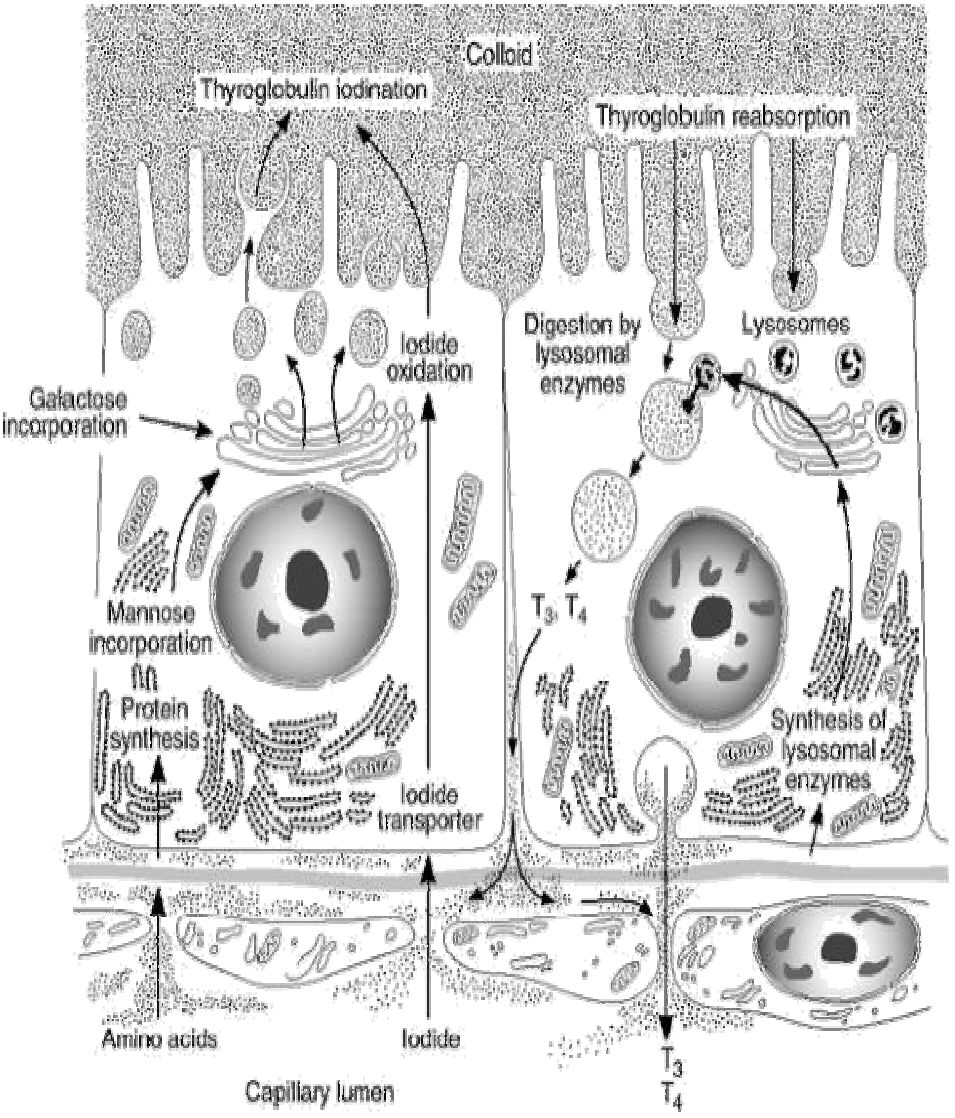
The recommendations of the World Health Organization for optimal daily iodide intake are as follows: for adults, 150 µg; during pregnancy and lactation, 200 µg; for the first year of life, 50 µg; for ages 1–6, 90 µg; and for ages 7–12, 120 µg. If iodide intake is below 50 µg/d, the gland is unable to maintain adequate hormonal secretion, and thyroid hypertrophy (goiter) and hypothyroidism result. In the United States, the average daily iodide intake increased from a range of 100–200 µg/d in the 1960s to 240–740 µg/d in the 1980s. This was largely due to the introduction of iodate as a dough conditioner, though other sources of dietary iodine included

iodized salt, vitamin and mineral preparations, iodine-containing medications, and iodinated contrast media[6]. In the 1990s, bromine salts replaced iodine in the baking industry, and iodine intake has fallen considerably, indicating the need for continued monitoring.

Iodide is rapidly absorbed from the alimentary tract and distributed in extracellular fluids as well as in salivary, gastric, and breast secretions[20]. Although the concentration of inorganic iodide in the extracellular fluid pool will vary directly with iodide intake, extracellular fluid I^- is usually quite low because of the rapid clearance of iodide from extracellular fluid by thyroidal uptake and renal clearance. In the example shown, the basal I^- concentration in extracellular fluid is only 0.6 µg/dl, or a sum of 150 µg of I^- in an extracellular pool of 25 L despite a daily oral intake of 500 µg I^-. In the thyroid gland there is energy mediated transport of I^- from the serum across the limiting membrane of the thyroid cell[20] .

The thyroid gland takes up about 115 µg of I^- per 24 hours, or, in this example, about 18% of the available I^-. About 75 µg of I^- is utilized for hormone synthesis and stored in thyroglobulin; the remaining iodide goes to extracellular fluid. The thyroid pool of organified iodine is very large, averaging 8–10 mg, and represents a store of hormone and iodinated tyrosines, protecting the organism against a period of iodine lack. From this storage pool, about 75 µg of hormonal iodide is released into the circulation daily[22]. This hormonal iodide is mostly bound to serum thyroxine-binding proteins, forming a circulating pool of about 600 µg of hormonal I^- (as T_3 and T_4). From this pool, about 75 µg of I^- as T_3 and T_4 is taken up and metabolized by tissues. About 60 µg of I^- is returned to the iodide pool and about

15 µg of hormonal I⁻ is conjugated with glucuronide or sulfate in the liver and excreted into the stool.. In the USA, the 24-hour thyroidal radioiodine uptake has decreased from about 40–50% in the 1960s to about 8–30% in the 1990s because of increased dietary iodide intake.



Processes of synthesis and iodination of thyroglobulin and its reabsorption and digestion

THYROID HORMONE PRODUCTION AND SECRETION

The production of thyroid hormone by the gland involves six steps[26]: (1) iodide trapping into the cell; (2) iodide oxidation & thyroglobulin iodination by tyrosyl residues; (3) T_3 and T_4 formation bycoupling of iodotyrosine in thyroglobulin ; (4) release of free iodothyronines and iodotyrosines by proteolysis; (5) iodotyrosines in the thyroid cell will be deiodonised and remanant iodide will be reused ; and (6) intrathyroidal 5′-deiodination of T_4 to T_3.

Thyroid hormone synthesis involves a unique glycoprotein, thyroglobulin, and an essential enzyme, thyroperoxidase (TPO).

THYROGLOBULIN

Thyroglobulin is a large glycoprotein molecule containing 5496 amino acids, with a molecular weight of about 660,000 and a sedimentation coefficient of 19S. It contains about 140 tyrosyl residues and about 10% carbohydrate in the form of mannose, N-acetylglucosamine, galactose, fucose, sialic acid, and chondroitin sulfate. The 19S thyroglobulin compound is a dimer of two identical 12S subunits, but small amounts of the 12S monomer and a 27S tetramer are often present. The iodine content of the molecule can vary from 0.1% to 1% by weight. In thyroglobulin containing 0.5% iodine (26 atoms of iodine per 660-kDa molecule), there would be 5 molecules of monoiodotyrosine (MIT), 4.5 molecules of diiodotyrosine (DIT), 2.5 molecules of thyroxine (T_4), and 0.7 molecules of triiodothyronine (T_3). About 75% of the thyroglobulin monomer consists of repetitive domains with no hormonogenic sites[14]. There are four tyrosyl sites for hormonogenesis on the thyroglobulin molecule: One site is located at the amino terminal end of the molecule, and the other three are

located in a sequence of 600 amino acids at the carboxyl terminal end. There is a surprising homology between this area of the thyroglobulin molecule and the structure of acetylcholinesterase, suggesting conservation in the evolution of these proteins.

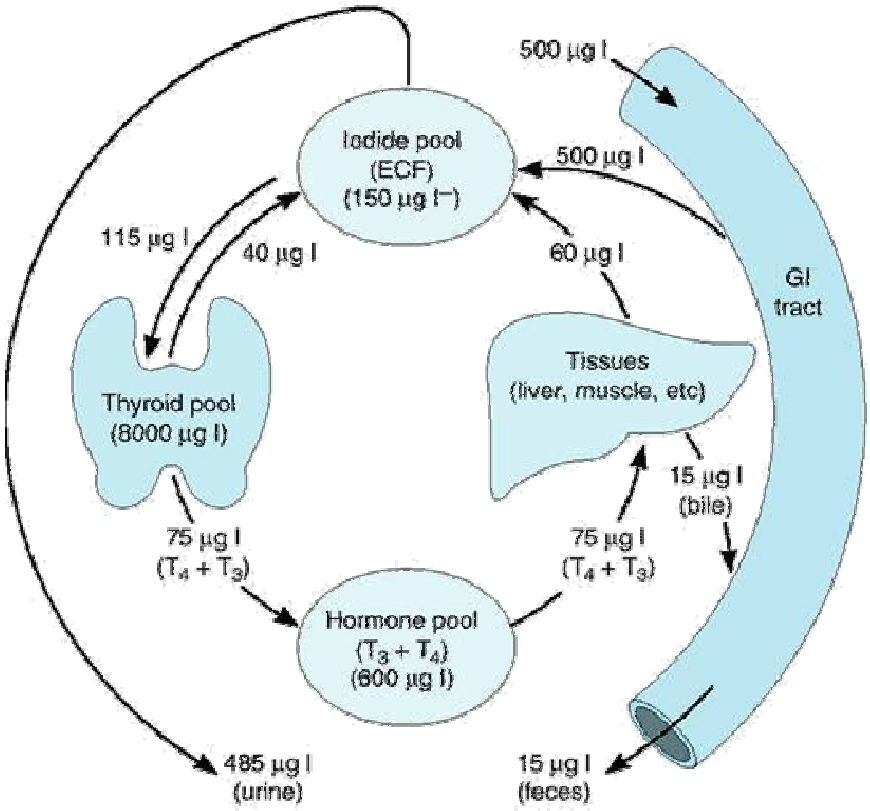
THYROIDAL PEROXIDASE

Thyroidal peroxidase is a membrane-bound glycoprotein with a molecular weight of about 102,000 and a heme compound as the prosthetic group of the enzyme. This enzyme mediates both the oxidation of iodide ions and the incorporation of iodine into tyrosine residues of thyroglobulin. Thyroidal peroxidase is synthesized in the rough endoplasmic reticulum (RER). After insertion into the membrane of RER cisternae, it is transferred to the apical cell surface through Golgi elements and exocytic vesicles. Here, at the cell colloid interface, it is available for iodination and hormonogenesis in thyroglobulin. Thyroidal peroxidase biosynthesis is stimulated by TSH

IODIDE TRANSPORT (THE IODIDE TRAP)

I^- is transported across the basement membrane of the thyroid cell by an intrinsic membrane protein called the Na^+/I^- symporter (NIS). At the apical border, a second I^- transport protein called pendrin moves iodine into the colloid where it is involved in hormonogenesis[18] . The NIS derives its energy from Na^+-K^+ ATPase, which drives the transport process. This active transport system allows the human thyroid gland to maintain a concentration of free iodide 30–40 times that in plasma. The NIS is stimulated by TSH and by the TSH receptor-stimulating antibody found in Graves' disease. It is saturable with large amounts of iodide and inhibited by ions such

as ClO_4^-, SCN^-, NO_3^-, and TcO_4^-. Some of these ions have clinical utility. Sodium perchlorate will discharge nonorganified iodide from the NIS and has been used to diagnose organification defects and in the treatment of iodide-induced hyperthyroidism. Sodium pertechnetate Tc99m, which has a 6-hour half-life and a 140-keV gamma emission, is used for rapid visualization of the thyroid gland for size and functioning nodules. Pendrin, encoded by the Pendred syndrome gene (PDS), is a transporter of chloride and iodide. Mutations in the PDS gene have been found in patients with goiter and congenital deafness (Pendred's syndrome). Although iodide is concentrated by salivary, gastric, and breast tissue, these tissues do not organify or store I^- and are not stimulated by TSH.



IODINE METABOLISM

IODINATION OF TYROSYL IN THYROGLOBULIN

Within the thyroid cell, at the cell-colloid interface, iodide is rapidly oxidized by H_2O_2, catalyzed by thyroperoxidase, and converted to an active intermediate which is incorporated into tyrosyl residues in thyroglobulin. H_2O_2 is probably generated by a dihydronicotinamide adenine dinucleotide phosphate (NADPH) oxidase in the presence of Ca^{2+}; this process is stimulated by TSH. The iodinating intermediate may be iodinium ion (I^+), hypoiodate, or an iodine-free radical. The site of iodination at the apical (colloid) border of the thyroid cell can be demonstrated by autoradiography[18]. Thyroidal peroxidase will catalyze iodination of tyrosyl molecules in proteins other than thyroglobulin, such as albumin or thyroglobulin fragments. However, no thyroactive hormones are formed in these proteins. The metabolically inactive protein may be released into the circulation, draining thyroidal iodide reserves.

COUPLING OF IODOTYROSYL RESIDUES IN THYROGLOBULIN

The coupling of iodotyrosyl residues in thyroglobulin is also catalyzed by thyroperoxidase[22]. It is thought that this is an intramolecular mechanism involving three processes: (1) iodotyrosyl residues is oxidized to an activated form by thyroperoxidase; (2) in thyroglobulin, coupling of iodotyrosyl residues to form a quinol ether intermediate; and (3) iodothyronine is formed by division of quinol ether. For this process to occur, the dimeric structure of thyroglobulin is essential: Within the thyroglobulin molecule T4 is formed by combining of two DIT molecules, and T3 by combining an MIT & DIT. Thiocarbamide drugs—particularly propylthiouracil, methimazole, and carbimazole—are potent inhibitors of thyroperoxidase and will block thyroid hormone synthesis . These drugs are

clinically useful in the management of hyperthyroidism.

PROTEOLYSIS OF THYROGLOBULIN & THYROID HORMONE SECRETION

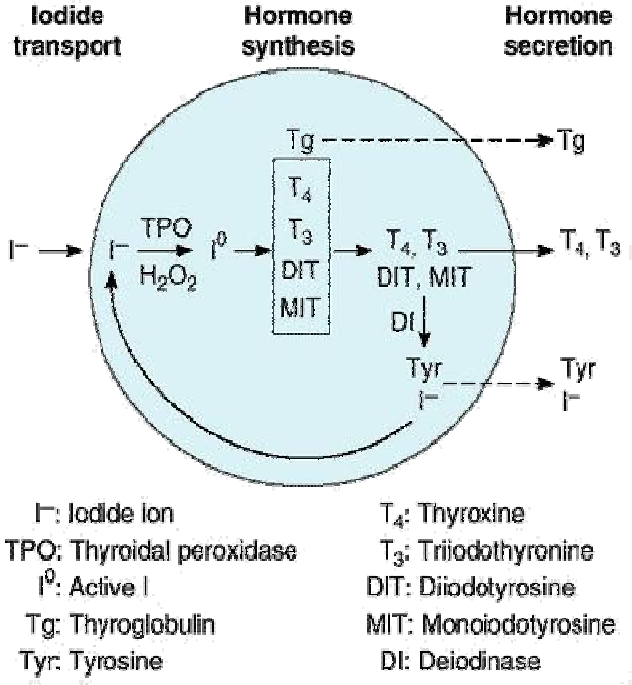
Rough endoplasmic reticulum secretes lysosomes and golgi apparatus packs it.These structures, surrounded by membrane, have an acidic interior and are filled with proteolytic enzymes, including proteases, endopeptidases, glycoside hydrolyases, phosphatases, and other enzymes[4]. At the cell-colloid interface, colloid is engulfed into a colloid vesicle by a process of macropinocytosis or micropinocytosis and is absorbed into the thyroid cell. The lysosomes then fuse with the colloid vesicle and thyroglobulin gets hydrolysed and it releases MIT,DIT,T3,T4 , peptide fragments, and amino acids. T_3 and T_4 are released into the circulation, while DIT and MIT are deiodinated and the I^- is conserved. Thyroglobulin with a low iodine content is hydrolyzed more rapidly than thyroglobulin with a high iodine content, which may be beneficial in geographic areas where natural iodine intake is low[4]. The mechanism of transport of T_3 and T_4 through the thyroid cell is not known, but it may involve a specific hormone carrier. TSH stimulates secretion of throid hormone by activating adenylyl cyclase and by the cAMP , suggesting that it is cAMP-dependent.

Large amount of iodide restricts thyroglobulin proteolysis like lithium , which, as lithium carbonate, is used for the treatment of bipolar disorders[1]. A little quantity of thyroglobulin which is not hydrolysed is secreted from the thyroid cell; this is markedly elevated in certain situations such as subacute thyroiditis, hyperthyroidism, or TSH-induced goiter . Thyroglobulin (perhaps modified) may also be synthesized and released by certain thyroid malignancies such as papillary or follicular thyroid

cancer and may be useful as a marker for metastatic disease.

INTRATHYROIDAL DEIODINATION

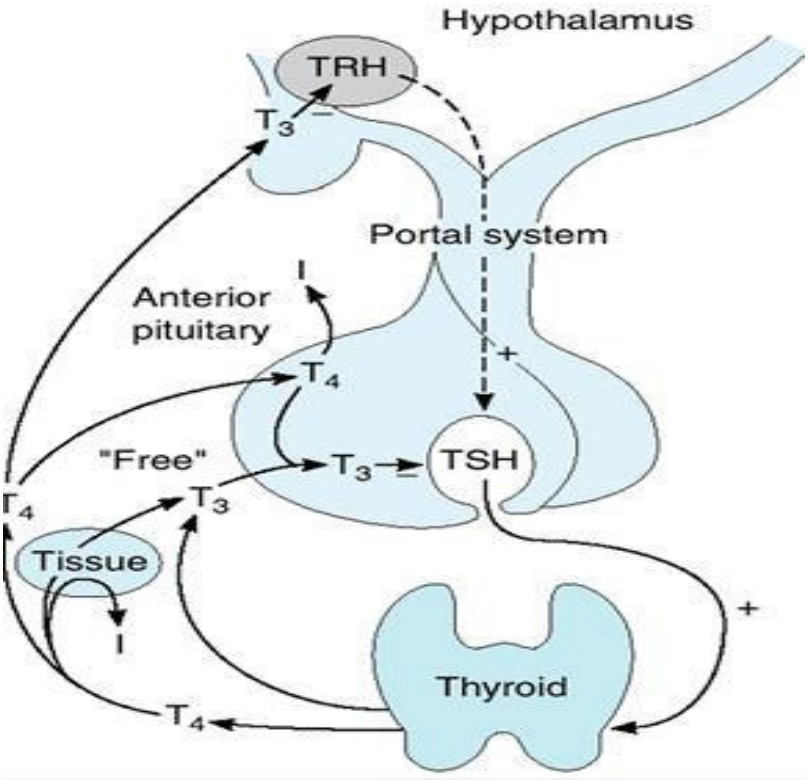
MIT and DIT formed during the synthesis of thyroid hormone are deiodinated by intrathyroidal deiodinase . This enzyme is an NADPH-dependent flavoprotein found in mitochondria and microsomes. It targets only o MIT and DIT but not on T_3 and T_4. The iodide released is reutilized for hormone synthesis. The 5′-deiodinase that converts T_4 to T_3 in peripheral tissues is also found in the thyroid gland. In situations of iodide deficiency, the activity of this enzyme may increase the amount of T_3 secreted by the thyroid gland, increasing the metabolic efficiency of hormone synthesis[15].



THYROID HORMONE SYNTHESIS IN A THYROID FOLLICLE

HIGHER CONTROL OF THYROID FUNCTION

development and function of the gland and thyroid hormones effects are managed by four mechanisms : (i) TSH , thyroid stimulating hormone synthesized by thyrotropic releasing hormone called as hypothalamic pituitary thyroid axis. Thyroid gland is then stimulated by TSH for its growth; (2)T3 & T4 actions are controlled by peripheral and pituitary deiodinases ; (3)thyroid gland has its own autoregulation for iodine demand;(4)Thyroid function is controlled by TSH receptor autoantibodies. In addition, the effects of T_3 may be modified by the status of the T_3 receptor (repressor or activation) and potentially by nonthyroidal T_3 receptor agonists or antagonists[12].



THE HYPOTHALAMIC-HYPOPHYSIAL-THYROIDAL AXIS

THYROTROPIN-RELEASING HORMONE

Thyrotropin-releasing hormone (TRH) is a tripeptide,

pyroglutamyl-histidyl-prolineamide, is formed in hypothalamus supraventricular & supraoptic nulei neurons. After formation it is kept in median eminence of hypothalamus. Then it travels to pituitary portal vein system to pituitary gland anterior for controlling synthesis of TSH secretion. The gene for human preproTRH, located on chromosome 3, contains a 3.3-kb transcription unit that encodes six TRH molecules. The gene also encodes other neuropeptides that may be biologically significant. In the anterior pituitary gland, TSH and prolactin are synthesized by binding of TRH to receptors in thyrotrophs and prolactin synthesizing cells. TRH response is decreased by thyroid hormone by slow process whereas estrogen increases TRH response by increasing sensitivity in pituitary[11].

The response of the pituitary thyrotroph to TRH is bimodal: First, it stimulates release of stored hormone; and second, it stimulates gene activity, which increases hormone synthesis. The TRH receptor (TRH-R) is a member of the seven-transmembrane-spanning, GTP-binding, protein-coupled receptor family. The TRHR gene is located on chromosome 8. Large glycoprotein hormones such as TSH and LH bind to the extracellular portions of their receptors, but TRH, a small peptide, binds to the transmembrane helix 3 of the TRH-R. After binding to its receptor on the thyrotroph, TRH activates a G protein, which in turn activates phospholipase c to hydrolyze phosphatidylinositol 4,5-bisphosphate (PIP_2) to inositol 1,4,5-trisphosphate

(IP_3). IP_3 stimulates the release of intracellular Ca^{2+}, which causes the first burst response of hormone release[27].

Simultaneously, there is generation of 1,2-diacylglycerol, which activates protein kinase C, thought to be responsible for the second and sustained phase of hormone secretion. The increases in intracellular Ca^{2+} and in protein kinase C may be involved in increased transcription of TSH. For ithyroid hormone full biologic activity it should be glycosylation of TSH which is stimulated by TRH.

THYROTROPIN

Thyroid-stimulating hormone, or thyrotropin (TSH), is a glycoprotein synthesized and secreted by the thyrotrophs of the anterior pituitary gland. It has a molecular weight of about 28,000 and is composed of two noncovalently linked subunits, α and β. The α subunit is common to the two other pituitary glycoproteins, FSH and LH, and also to the placental hormone hCG; the β subunit is different for each glycoprotein hormone and confers specific binding properties and biologic activity[10]. The human α subunit has an apoprotein core of 92 amino acids and contains two oligosaccharide chains; the TSH β subunit has an apoprotein core of 112 amino acids and contains one oligosaccharide chain.

The α and β subunit amino acid chains of TSH each form “cysteine knot” by joining three coils which are interrupted. Mutations of the amino acids in either chain can result in either decreased or increased TSH activity. Glycosylation takes place in the rough ER and the Golgiapparatus of the thyrotroph, where glucose, mannose, and fucose residues and terminal sulfate or sialic acid residues are linked

to the apoprotein core. The function of these carbohydrate residues is not entirely clear, but it is likely that they enhance TSH biologic activity and modify its metabolic clearance rate[8]. For example, deglycosylated TSH will bind to its receptor, but its biologic activity is markedly decreased and its metabolic clearance rate is markedly increased.

Thyroid hormone production is controlled by mainly TSH. This is attained by binding of TSH with its receptor called TSH-R which is unique and then it causes triggering of cAMP . The human TSH receptor (TSH-R) gene is located on chromosome 14q3. The TSH-R is a single-chain glycoprotein containing 764 amino acids. Like the TRH receptor of the anterior pituitary, the TSH-R in the thyroid follicular cell is a member of the seven-membrane spanning, GTP-binding protein-coupled receptor family. Structurally, it can be divided into two subunits: subunit A, containing 397 amino acids, representing the ectodomain which is involved in ligand binding; and subunit B, which includes the intramembrane and intracellular portion of the receptor involved in action of thyroid development, hormone production, and its release[9]. The TSH-R is unique in that it has binding sites not only for TSH but also for TSH receptor antibody, which are found in patients with autoimmune hyperthyroidism (Graves' disease), and also for autoantibodies that bind to the TSH receptor and block the action of TSH (TSH-R Ab [block]). These antibodies are also found in hypothyroidism and some thyroiditis

Mutations in the TSH-R have been associated with either spontaneous activation of the receptor and clinical hyperthyroidism or with resistance to TSH. Activating mutations involving the B subunit of the TSH-R have been found in

solitary autonomous adenomas and in multinodular goiters as well as in rare cases of sporadic familial hyperthyroidism. Resistance to TSH due to mutations in either subunit of the receptor is related to high TSH levels.

THE ACTION OF THYROID HORMONES

1. THE THYROID HORMONE RECEPTOR

Thyroid hormones, T_3 and T_4, circulate in plasma largely bound to protein but in equilibrium with the free hormone. It is the free hormone that is transported, either by passive diffusion or by specific carriers, through the cell membrane, through the cell cytoplasm, to bind to a specific receptor in the cell nucleus. Inside the cell, T_4 is changed to T_3 by 5' deiodinase, implicating that T_4 is a proactive and T_3 the functional form of the hormone[31]. In the human, there are two genes for the thyroid hormone receptor, alpha and beta. TRα is located on chromosome 17 and TRβ on chromosome 3. Each gene produces at least two products, TRα 1 and 2 and TRβ 1 and 2. Each has three domains: a ligand-independent domain at the amino terminal, a centrally located DNA binding area with two cysteine-zinc "fingers," and a ligand-binding domain at the carboxyl terminal. Note that TRα2 does not bind T_3 and may actually inhibit T_3 action.The concentration of these receptors in tissue varies with the stage of development and the tissue. For example, the brain contains mostly TRα, the liver mostly TRβ, and cardiac muscle contains both. The binding affinity of T_3 analogs is directly proportionate to the biologic activity of the analog. Point mutations in the ligand-binding domain of the TRβ gene are responsible for the syndrome of generalized resistance to thyroid hormone.

The thyroid hormone receptors may bind to the specific thyroid hormone response element (TRE) sites on DNA even in the absence of T_3 (— unlike the steroid hormone receptors). The TREs are located near—generally upstream with respect to the start of transcription—to the promoters where transcription of specific thyroid hormone-responsive genes is initiated. T_3 binding to the receptors results in stimulation—in some cases inhibition—of the transcription of these genes with consequent changes in the levels of the mRNAs transcribed from them. The changes in mRNA levels alter the levels of the protein product of these genes[35]. These proteins then mediate the thyroid hormone response. These receptors often function as heterodimers with other transcription factors such as the retinoid X receptor and the retinoic acid receptor.

3. PHYSIOLOGIC EFFECTS OF THYROID HORMONES

The transcriptional effects of T_3 characteristically demonstrate a lag time of hours or days to achieve full effect. These genomic actions result in a number of effects, including those on tissue growth, brain maturation, and increased heat production and oxygen consumption, which is due in part to increased activity of Na^+-K^+ ATPase and in part to production of increased beta-adrenergic receptors. Some actions of T_3 are not genomic, such as reduction of pituitary type 2 5′-deiodinase and increase in glucose and amino acid transport[37]. Some specific effects of thyroid hormones are summarized in what follows.

EFFECTS ON FETAL MATURATION

At fetal life of 11 weeks itself TSH and thyroid hormones will begin their functions. Because of the high placental content of type 3 5-deiodinase, most

maternal T_3 and T_4 are inactivated in the placenta, and very little free hormone reaches the fetal circulation. This little quantity of available hormoneis essential for fetal brain maturation. However, after 11 wks of pregnancy, the fetus is largely dependent on its own thyroidal secretion. Although some fetal growth occurs in the absence of fetal thyroid hormone secretion, brain development and skeletal maturation are markedly impaired, resulting in cretinism (mental retardation and dwarfism).

EFFECTS ON OXYGEN CONSUMPTION, HEAT PRODUCTION, & FREE RADICAL FORMATION

T_3 increases O_2 consumption and heat production in part by stimulation of Na^+-K^+ ATPase in all tissues except the brain, spleen, and testis. This contributes to the increased basal metabolic rate (O_2 consumption by the whole animal at rest) and the increased sensitivity to heat in hyperthyroidism— and the converse in hypothyroidism[37]. Thyroid hormones also decrease superoxide dismutase levels, resulting in increased superoxide anion free radical formation. This may contribute to the deleterious effects of chronic hyperthyroidism.

CARDIOVASCULAR EFFECTS

T_3 induces transcription of α part of myosin heavy chain and depresses β heavy chain, making more cardiac muscle contractility. In addition T_3 fastens transcription of Ca^{2+} ATPase in the sarcoplasmic reticulum, raising diastolic tone of the heart; changes isoforms of Na^+-K^+ ATPase genes; and raises beta-adrenergic receptors and the concentration of G proteins. So , thyroid hormones have marked positive inotropic

and chronotropic effects on the heart. This makes , there is high cardiac output & hear rate in hyperthyroidism whereas low in hypothyroidism.

SYMPATHETIC EFFECTS

Thyroid hormones raises more number of beta-adrenergic receptors in heart & skeletal muscle, adipose tissue, and lymphocytes. It also slows the myocardial alpha-adrenergic receptors[38]. They also may accelerate catecholamine action at a postreceptor site. Thus, response to catecholamines is more pronounced in hyperthyroidism, and treatment with beta-adrenergic blocking agents may be very helpful in controlling tachycardia and arrhythmias.

PULMONARY EFFECTS

Thyroid hormones maintain normal oxygen and carbondioxide demand by keeping respiratory centre active. In severe hypothyroidism, hypoventilation occurs, occasionally requiring assisted ventilation.

HEMATOPOIETIC EFFECTS

The increased cellular demand for O_2 in hyperthyroidism leads to increased production of erythropoietin and increased erythropoiesis. However, blood volume is usually not increased because of hemodilution and increased red cell turnover[14]. Thyroid hormones increase the 2,3-diphosphoglycerate content of erythrocytes, so that it makes more displacement of O_2 from haemoglobin to tissues. The reverse occurs in hypothyroidism.

GASTROINTESTINAL EFFECTS

Thyroid hormones stimulate gut motility, which can result in increased motility and diarrhea in hyperthyroidism and slowed bowel transit and constipation in hypothyroidism[19]. This may also contribute to the modest weight loss in hyperthyroidism and weight gain in hypothyroidism.

SKELETAL EFFECTS

Thyroid hormones stimulate increased bone turnover, increasing bone resorption and, to a lesser degree, bone formation. Thus, chronic hyperthyroidism may result in significant osteopenia and, in severe cases, modest hypercalcemia, hypercalciuria, and increased excretion of urinary hydroxyproline and pyridinium cross-links.

NEUROMUSCULAR EFFECTS

Although thyroid hormones stimulate increased synthesis of many structural proteins, in hyperthyroidism there is increased protein turnover and loss of muscle tissue, or myopathy. This may be associated with spontaneous creatinuria. Increased reflexes in hyperthyroidism is due to fast muscle contraction and relaxation or the reverse in hypothyroidism. Thyroid hormones are essential for normal development and function of the central nervous system, and failure of fetal thyroid function results in severe mental retardation. In the adult, hyperactivity in hyperthyroidism and sluggishness in hypothyroidism can be striking.

EFFECTS ON LIPID & CARBOHYDRATE METABOLISM

Hyperthyroidism increases liver glucose production and glycogen breakdown as well as gut glucose absorption. Thus, hyperthyroidism will exacerbate underlying diabetes mellitus. Cholesterol synthesis and degradation are both increased by thyroid hormones. The latter effect is due largely to an increase in the hepatic low-density lipoprotein (LDL) receptors, so that cholesterol levels decline with thyroid overactivity. Lipolysis is also increased, releasing fatty acids and glycerol. Conversely, cholesterol levels are elevated in hypothyroidism.

ENDOCRINE EFFECTS

Thyroid hormones increase the metabolic turnover of many hormones and pharmacologic agents. Increases the half life of cortisol[15]. The production rate of cortisol will increase in the hyperthyroid patient with normal adrenal function, thus maintaining a normal circulating hormone level. However, in a patient with adrenal insufficiency, the development of hyperthyroidism or thyroid hormone treatment of hypothyroidism may unmask the adrenal disease. Ovulation may be impaired in both hyperthyroidism and hypothyroidism, resulting in infertility, which will be corrected by restoration of the euthyroid state. Serum prolactin levels are increased in about 40% of patients with hypothyroidism, presumably a manifestation of increased TRH release; this will revert to normal with T_4 therapy..

TESTS OF THYROID FUNCTION

The function of the thyroid gland may be evaluated in many different ways:

(1) blood level of thyroid hormones,

(2) study of the hypothalamic-pituitary-thyroid axis,

(3) evaluation of iodine metabolism,

(4) gland size measurement,

(5) biopsy of gland,

(6) action on peripheral tissues by thyroid hormone,

(7) magnitude of thyroid autoantibodies.

TESTS OF THYROID HORMONES IN BLOOD

The total serum T_4 and total serum T_3 are measured by radioimmunoassay or immunofluorescent assay[42]. If the concentration of serum thyroid hormone binding proteins is normal, these measurements provide a reasonably reliable index of thyroid gland activity. However, changes in serum concentration of thyroid-binding proteins or the presence of drugs that modify the binding of T_4 or T_3 to TBP will modify the total T_4 and T_3 but not the amount of free hormone. Thus, further tests must be performed to assess the free hormone level that determines biologic activity.

Serum free thyroxine (FT_4) can be estimated using the free thyroxine index (FT_4I). This is the product of the total T_4 multiplied by the percentage of free T_4 as estimated by the amount of T_4 which binds to resin or

charcoal added to the system. A more precise estimate of free thyroxine is obtained by

a two-step chemiluminescent immunoassay in which the thyroxine antibody system is modified to react with the free hormone. The normal range for FT_4 by this assay is 0.7–1.85 ng/dL (9–24 pmol/L). Although the FT_4I or the FT_4 is valid for normal subjects, these assays may not be valid in subjects with dysproteinemias and abnormal thyroxine-binding proteins (TBPs)—or in subjects taking medications modifying TBP or in subjects with the euthyroid sick syndrome[46]. In these subjects, free thyroxine by equilibrium dialysis (FT_4D) will more accurately reflect the level of free thyroxine. Note that FT_4 does not measure T_3, so that patients receiving high oral doses of T_3 or with T_3 hyperthyroidism , FT_4 may be low despite the hyperthyroid state (T_3 toxicosis). Antiepileptic drugs such as phenytoin and carbamazepine and the antituberculous drug rifampin increase hepatic metabolism of T_4, resulting in a low total T_4, a low free T_4, and a low FT_4I. However, serum T_3 and serum TSH levels are normal, indicating that patients receiving these drugs are euthyroid. T_4 and FT_4I may be low in severe illness, but FT_4D and TSH are usually normal, which will distinguish these very ill patients from patients who are hypothyroid.

At times, FT_4I and FT_4D will be inappropriately elevated. For example, drugs such as iodinated contrast media, amiodarone, glucocorticoids, and propranolol inhibit type 1 5′-deiodinase and the conversion of T_4 to T_3 in peripheral tissues, resulting in elevation of total T_4, FT_4I, and FT_4D and depression of T_3. Hyperthyroidism is ruled out by the low T_3 and normal TSH[44]. FT_4I and FT_4D are inappropriately elevated in the rare syndrome of generalized resistance to thyroid hormone . The presence of heparin in serum, even in the tiny amounts that would be found in a patient with a “heparin lock” indwelling intravenous catheter, will cause a

spurious increase in FT_4D. This occurs in the test tube, since heparin activates lipoprotein lipase, releasing free fatty acids that displace T_4 from TBG.

Total T3 can be measured in serum by immunoassay with specific T_3 antisera. The normal range in adults is 70–132 ng/dL (1.1–2 nmol/L). The measurement of total T_3 is most useful in the differential diagnosis of hyperthyroidism, because T_3 is preferentially secreted in early Graves' disease or toxic nodular goiter. In hyperthyroidism, this ratio will usually be well over 20, and it will be even higher in T_3 thyrotoxicosis. T_3 levels are often maintained in the normal range in hypothyroidism because TSH stimulation increases the relative secretion of T_3; thus, serum T_3 is not a good test for hypothyroidism.

T_3 is bound to TBG, and the total T_3 concentration in serum will vary with the level of TBG. Serum free T_3 (FT_3) can be measured by immunoassay or more precisely by equilibrium dialysis; the normal adult FT_3 is 230–420 pg/dL (3.5–6.5 pmol/L).

Reverse T_3 (rT_3) can be measured by radioimmunoassay. The serum concentration of rT_3 in adults is about one-third of the total T_3 concentration, with a range of 25–75 ng/dL (0.39–1.15 nmol/L). RT_3 can be used to differentiate chronic illness from hypothyroidism because rT_3 levels are elevated in chronic illness and low in hypothyroidism. However, this differential diagnosis can be made by determination of TSH (see below), so that it is rarely necessary to measure rT_3[40].

Thyroglobulin(Tg) can be measured in serum by double antibody radioimmunoassay. The normal range will vary with method and laboratory, but

generally the normal range is less than 40 ng/mL (< 40 µg/L) in the euthyroid individual and less than 2 ng/mL (< 2 µg/L) in a totally thyroidectomized individual. The major problem with the test is that endogenous thyroglobulin antibodies interfere with the assay procedure and, depending on the method, may result in spuriously low or spuriously high values. Serum thyroglobulin is elevated in situations of thyroid overactivity such as Graves' disease and toxic multinodular goiter; in subacute or chronic thyroiditis, where it is released as a consequence of tissue damage; and in patients with large goiters, in whom the thyroglobulin level is proportionate to the size of the gland. Serum thyroglobulin determinations have been most useful in the management of patients with papillary or follicular thyroid carcinoma. Following thyroidectomy and ^{131}I therapy, thyroglobulin levels should be very low. In such a patient, serum thyroglobulin greater than 2 ng/dL (> 2 µg/L) indicates the presence of metastatic disease, and a rise in serum thyroglobulin in a patient with known metastases indicates progression of the disease.

EVALUATION OF THE HYPOTHALAMIC-PITUITARY-THYROID AXIS

It has not been clinically feasible to measure TRH in the peripheral circulation in humans. However, very sensitive methods for the measurement of TSH have been developed using monoclonal antibodies against human TSH. The general principle is this: One monoclonal TSH antibody is fixed to a solid matrix to bind serum TSH, and a second monoclonal TSH antibody labeled with isotope or enzyme or fluorescent tag will bind to a separate epitope on the TSH molecule. The quantity of TSH in the serum is thus proportionate to the quantity of bound second antibody. The earlier TSH radioimmunoassays, which could detect about 1 μU of TSH/mL, were adequate for the diagnosis of elevated TSH in hypothyroidism but could not detect suppressed TSH levels in hyperthyroidism. The "second generation" of "sensitive" TSH assays, using monoclonal antibodies, can detect about 0.1 μU/mL, and the "third generation" of "supersensitive" assays are sufficiently sensitive to detect about 0.01 μU/mL. This has allowed measurement of TSH well below the normal range of 0.5–5 μU/mL (0.5–5 mU/L) and has enabled the clinician to detect partially and totally suppressed serum TSH levels. The level of FT_4 is inversely related to the logarithm of the TSH concentration . Thus, a small change in FT_4 may result in a large change in TSH. Serum TSH below 0.1 μU/mL (0.1 mU/L) and an elevated FT_4 or FT_4I is indicative of hyperthyroidism. This may be due to Graves' disease, toxic nodular goiter, or high-dose thyroxine therapy. In the rare case of hyperthyroidism due to a TSH-secreting pituitary tumor, FT_4I or FT_4

will be elevated and TSH will not be suppressed but will actually be normal or slightly elevated. An elevated TSH (> 10 μU/mL; 10 mU/L) and a low FT_4 or FT_4I is diagnostic of hypothyroidism. In patients with hypothyroidism due to a pituitary or hypothalamic tumor (central hypothyroidism), FT_4I or FT_4 will be low and TSH will not be elevated. This diagnosis can be confirmed by demonstrating the failure of serum TSH to increase following an injection of TRH. The TRH test is performed as follows: 200 μg of TRH is administered intravenously. Serum TSH is measured before to the injection and after half an hour and an hour afterward. The absence of a rise in TSH indicates either pituitary insufficiency or suppression. A modest or delayed rise may be seen in patients with hypothalamic disease and hypothyroidism. The test can also be used to differentiate the hyperthyroxinemia of the T_3 resistance syndrome from thyrotoxicosis due to a TSH-secreting pituitary tumor. TRH will produce a rise in TSH in the patient with a thyroid hormone resistance syndrome, whereas TSH-secreting tumors will not respond to TRH. Note that corticosteroids and dopamine inhibit TSH secretion , which will modify the interpretation of serum TSH levels in patients taking these drugs.

Serum TSH levels reflect the anterior pituitary gland sensing the level of circulating FT_4. High FT_4 levels suppress TSH and low FT_4 levels increase TSH release. Thus, the ultrasensitive measurement of TSH has become the most sensitive, most convenient, and most specific test for the diagnosis of both hyperthyroidism and hypothyroidism. Indeed, a suppressed TSH correlates so well with impaired pituitary response to TRH that the simple measurement of serum TSH has replaced the TRH test in the diagnosis of hyperthyroidism.

IODINE METABOLISM & BIOSYNTHETIC ACTIVITY

Radioactive iodine allows assessment of the turnover of iodine by the thyroid gland in vivo. Iodine-123 is the ideal isotope for this purpose: It has a half-life of 13.3 hours and releases a 28-keV x-ray and a 159-keV gamma photon but no beta emissions. Thus, it is easily measured and causes little tissue damage. It is usually administered orally in a dose of 100–200 μCi, and radioactivity over the thyroid area is measured with a scintillation counter at 4 or 6 hours and again at 24 hours . The normal radioactive iodine uptake (RAIU) will vary with the iodide intake. In areas of low iodide intake and endemic goiter, the 24-hour RAIU may be as high as 60–90%. In hyperthyroidism due to Graves' disease or toxic nodular goiter, the 24-hour radioactive iodine uptake is markedly elevated, though if the iodide turnover is very rapid, the 5-hour uptake may be even higher than the 24-hour uptake[44].

Thyrotoxicosis with a very low thyroidal RAIU occurs in the following situations: (1) in subacute thyroiditis; (2) during the active phase of Hashimoto's thyroiditis, with release of preformed hormone, causing “spontaneously resolving thyrotoxicosis”; (3) in thyrotoxicosis factitia due to oral ingestion of a large amount of thyroid hormone; (4) as a result of excess iodide intake (eg, amiodarone therapy), inducing thyrotoxicosis in a patient with latent Graves' disease or multinodular goiter, the low uptake being due to the huge iodide pool; (5) in struma ovarii; and (6) in ectopic functioning metastatic thyroid carcinoma after thyroidectomy.

Test	Symbol	Normal Range
Thyroxine	T4	4.5-12 µg/dL
Thiiodothyronine	T3	90-200 ng/dL
Thyroid-stimulating hormone	TSH	0.4-4.5 µIU/mL
Free T4	FT4	0.7-1.6 ng/dL
Free T3	FT3	230-420 ng/L
Iodine-131 uptake	RAIU	8%-35% at 24 h

THYROID IMAGING

1. RADIONUCLIDE IMAGING

I^{123} and technetium Tc 99m pertechnetate (^{99m}Tc as TcO_4) are useful for determining the functional activity of the thyroid gland. ^{123}I is administered orally in a dose of 200–300 µCi, and a scan of the thyroid is obtained at 8–24 hours. $^{99m}TcO_4$ is administered intravenously in a dose of 1–10 mCi, and the scan is obtained at 30–60 minutes. Images can be obtained with either a rectilinear scanner or a gamma camera. The rectilinear scanner moves back and forth over the area of interest; it produces a life-size picture, and special areas, such as nodules, can be marked directly on the scan [46]. The gamma camera has a pinhole collimator, and the scan is obtained on a fluorescent screen and recorded on Polaroid film or a computer monitor. The camera has greater resolution, but special areas must be identified with a radioactive marker for clinical correlation . Radionuclide scans provide information about both the size

and shape of the thyroid gland and the geographic distribution of functional activity in the gland. Functioning thyroid nodules are called “hot” nodules, and those not functioning are stated “cold” nodules. The malignancy accounts only less tthan 1% as hot nodules and they turn into toxic and cause thyrotoxicosis. . Among cold nodules 16% were malignant. Occasionally, a nodule will be hot with $^{99m}TcO_4$ and cold with ^{123}I, and a few of these nodules have been malignant. ^{131}I is the preferred isotope for huge substernal goiter & for distant metastases.

2. FLUORESCENT SCANNING

The iodine content can be determined and an image of the thyroid gland can be obtained by fluorescent scanning without administration of a radioisotope. An external source of americium-241 is beamed at the thyroid gland, and the resulting emission of 28.5 keV x-ray from iodide ions is recorded, producing an image of the thyroid gland similar to that obtained with^{123}I. The advantage of this procedure is that the patient receives no radioisotope[33] and the gland can be imaged even when it is loaded with iodine—as, for example, after intravenous contrast media. The disadvantage of this study is that it requires specialized equipment that may not be generally available.

THYROID ULTRASONOGRAPHY OR MAGNETIC RESONANCE IMAGING

A rough estimate of thyroid size and nodularity can be obtained from radionuclide scanning, but much better detail can be obtained by thyroid

ultrasonography or MRI. USG of thyroid is helpful in finding the size of gland or nodular size and for assessment of treatment. It is helpful also for differentiating cystic lesions from solid one. Substernal goiter cannot be assessed by USG.

MRI has more advanced technique and gives good picture of thyroid gland, posterior or substernal extension pathology. Both transverse and coronal images of the gland can be obtained, and lymph nodes as small as 1 cm can be visualized. MRI is not useful in tracheal compression from a huge goiter, tracheal invasion by thyroid tumours, or metastases to lymph nodes.

THYROID BIOPSY

The best procedure for differentiating from benign and malignant disease is Fine-needle aspiration biopsy. It is a simple to perform and no admission required. The skin over the nodule is cleansed with alcohol, and, if desired, a small amount of 1% lidocaine can be injected intracutaneously for local anesthesia. A No. 25 3.75 cm needle is pierced in the gland and moved to and fro till a little quantity of blood comes in needle and it is taken out., and with a syringe the contents of the needle is put onto a sterile slide. A second clean slide is placed on top of the first slide, and a thin smear is obtained by drawing the slides apart quickly. Alternatively, a 10 mL or 20 mL syringe in an appropriate syringe holder can be used with a No. 23 one-inch needle to sample the nodule or to evacuate cystic contents.

Using Wright's or Giemsa's stain, fixed in alcohol and with Papanicolaou stain slides are fixed or made dry.The sensitivity (true-positive results divided by total cases of disease) is about 95%, and the specificity (true-negative results divided by

total cases of no disease) is also about 95%. For best results, fine-needle aspiration biopsy it needs a fair amount of sample and cytologist experience.

HYPOTHYROIDISM

Hypothyroidism (Greek, from *hypo*, under, and *thyroid*, the gland), often called underactive thyroid or low thyroid, is an endocrine abnormality which occurs commonly in which the thyroid gland is not able to produce enough thyroid hormones[28].

In overt primary hypothyroidism the TSH levels are high and the T_4 &T_3 levels are low.[21] It is also diagnosed in those who have a TSH value of greater than IU/L with symptoms of hypothyroid and borderline T4 values. In persons with a TSH greater than 10mIU/L it is diagnostic of hypothyroid.[21]

Subclinical hypothyroidism is a milder form characterized by an elevated serum TSH level, but a normal serum free thyroxine level.[22, 23] In adults it is diagnosed when TSH levels are greater than 5 mIU/L and less than 10mIU/L.[21]

Deficiency of iodine is the most common cause of hypothyroidism worldwide. In those areas in which iodine is sufficient, autoimmune disease (Hashimoto's thyroiditis) and other iatrogenic causes must be evaluated for.[10]

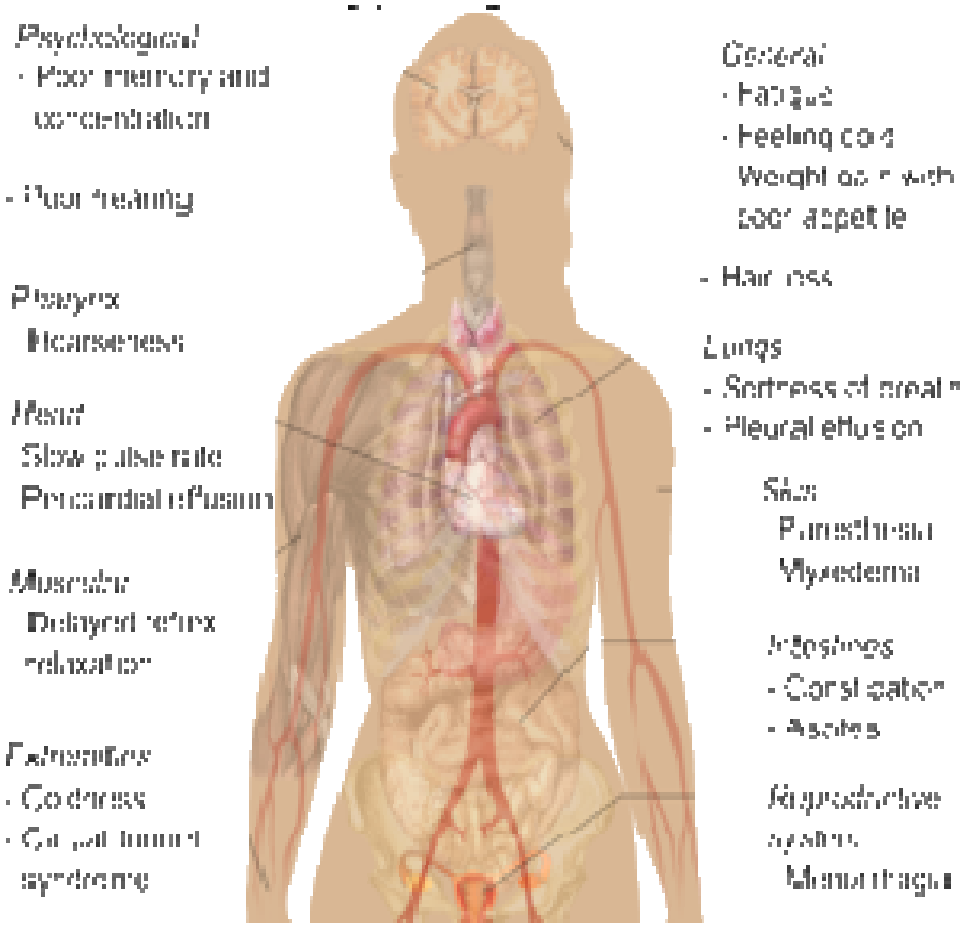


Fig: Signs and Symptoms of Hypothyroidism

Causes of Hypothyroidism	
Central (Hypothalamic/Pituitary) Hypothyroidism	
Loss of functional hypothalamic or pituitary tissue	• Tumor (pituitary adenomas, metastasis, craniopharyngioma, glioma) • Trauma (surgeries, irradiation and head injury) • Vascular (Ischemic necrosis, hemorrhage, aneurysms) • Infections (TB, abscess) • Infiltrative lesions (sarcoidosis) • Chronic lymphocytic hypophysitis • Congenital (pituitary hypoplasia, basal encephalocele)
Functional defects in TSH biosynthesis and release	• Gene mutation • Drug-induced (dopamine, glucocorticoids)
Primary Hypothyroidism	
Loss of functional thyroid tissue	• Chronic autoimmune thyroiditis (Hashimoto's thyroiditis) • Reversible autoimmune hypothyroidism (painless and postpartum thyroiditis, cytokine-induced thyroiditis). • Surgery (thyroidectomy) • Radiation (I-131 or external irradiation) • Infiltrative and infectious diseases, sub-acute thyroiditis • Congenital defects (thyroid dysgenesis)
Functional defects in thyroid hormone biosynthesis and release	• Congenital defects in thyroid hormone biosynthesis • Iodine deficiency and iodine excess • Drug-induced (antithyroid agents, lithium, amiodarone)

TABLE 1 Signs and symptoms of hypothyroidism

Signs	Symptoms*
Hypothermia	Fatigue
Bradycardia	Weakness
Delayed relaxation of deep tendon reflexes	Weight gain
Periorbital edema	Constipation
Enlargement of tongue	Cold intolerance
Diastolic hypertension	Dry skin
Hair loss	Hoarse voice
Pleural and pericardial effusions	Edema
	Cognitive dysfunction
	Depression
	Muscle cramps
	Paresthesias
	Menorrhagia
	Dry, gritty-feeling eyes

* Patients rarely report these symptoms spontaneously. It is therefore important for the clinician to complete a thorough review of systems.

Laboratory Evaluation:

If the TSH level is normal, then the diagnosis of primary hypothyroidism is ruled out[22]. If TSH level is elevated, then the level of unbound T4 must be obtained to confirm clinical hypothyroidism. However as a screening test TSH is superior to T4 because it will detect subclinical hypothyroidism. Unbound T3 levels are normal in 25% of patients, showing adaptive de-iodinase response to hypothyroidism; hence measurement of T3 is not indicated.

Once hypothyroidism is diagnosed the presence of TPO antibodies must be searched to demonstrate the etiology. TPO antibodies are present in about 90% of the patients

who suffer from autoimmune hypothyroidism. TBII is found in 10–20% of patients however we do not perform this test routinely.[10]

Free thyroxine levels in pregnant women will be lower than expected because of decreased binding of free thyroxine to albumin and because of increased binding of free thyroxine to thyroid binding globulin. Hence total thyroxine levels must be used for diagnosis.[5] TSH values be less than the normal range in pregnancy and must be adjusted for the period of pregnancy.[5, 19]

There is a low sodium level in blood along with raised antidiuretic hormone and there is as acute worsening of kidney function due to several causes in patients suffering from very severe hypothyroidism and myxedema coma.

When thyroxine is replaced, it leads to anaemia and other derangements[1, 6]. Other laboratory findings which are abnormal in hypothyroidism are anaemia (usually normocytic or macrocytic), elevated cholesterol and triglycerides and increased creatine phosphokinase.

		Sensitive TSH		
		Normal	Low	High
T_4	Normal	Euthyroid	Subclinical/early hyperthyroidism[a] Nonthyroidal illness Drug effects L-dopa Glucocorticoids Excess T_4 therapy for hypothyroidism	Subclinical/early hypothyroidism Nonthyroidal illness Drug effects Iodine, lithium, antithyroid drugs, amiodarone Insufficient T_4 therapy for hypothyroidism
	Low	Secondary hypothyroidism[b] Nonthyroidal illness Drug effects T_3 Phenytoin Androgens Salicylates Carbamazepine Rifampin	Secondary hypothyroidism[b] Drug effects Dopamine[c] Corticosteroids[c] T_3	Primary hypothyroidism Drug effects, e.g., iodine, lithium, antithyroid drugs, amiodarone Insufficient T_4 therapy for hypothyroidism
	High	Nonthyroidal illness Acute and psychiatric illness Abnormal binding (excess TBG, familial dysalbuminemic hyperthyroxinemia, transthyretin-associated hyperthyroxinemia, some monoclonal proteins) Thyroid hormone resistance Drug effects Estrogen Iodine (drugs, contrast media) Thyroxine (factitious)	Nonthyroidal illness Acute psychiatric illness Primary hyperthyroidism[d]	TSH-secreting tumor Thyroid hormone resistance

T_3 = triiodothyronine; T_4 = thyroxine.
[a]Confirm with T_3 suppression test or lack of serum TSH response to TRH.
[b]Pituitary TSH deficiency shows deficient response to exogenous TRH. Hypothalamic TRH deficiency shows normal TSH response but may be prolonged for >30 mins.
[c]Serial monitoring or testing of serum TSH response to TRH may be needed.
[d]95% of cases; serum T_3 needed for diagnosis of T_3 thyrotoxicosis.

Entity tested	Description	Clinical utility
TSH	Thyroid-stimulating hormone or thyrotropin	• Best thyroid function screening test • Initial test for suspected thyroid disease • Used to follow patients on thyroid hormone therapy • Used in conjunction with T_4 to manage patients with Graves' disease
T_4	Serum total thyroxine	• Used to make diagnosis of underactive or overactive thyroid when TSH is abnormal • Used with TSH for monitoring patients with Graves' disease • Newborn screening test for hypothyroidism • Fairly accurate in patients with no protein abnormalities and not pregnant
FT_4	Free thyroxine is the metabolically active thyroid hormone – not bound to protein	• Should be ordered when TSH is abnormal to determine thyroid hyperfunction or hypofunction.
FTI	Free thyroxine index – measure of free T_4 determined by measuring thyroxine level and either thyroid-binding globulin or hormone-binding ratio	• Used for making the diagnosis of thyroid disease in patients with protein abnormalities and in pregnant patients • Used for monitoring therapy in above patient groups with hyperthyroidism
T_3	Serum total triiodothyronine	• Used to diagnose hyperthyroidism when TSH is low and T_4 is still normal
Thyroid antibodies	• Antithyroid peroxidase (antimicrosomal) antibodies • Antithyroglobulin antibodies	• Used to diagnose suspected Hashimoto's thyroiditis in hypothyroidism • Used to diagnose autoimmune thyroiditis or Graves' disease in hyperthyroidism

Sources: Baskin HJ et al[2]; Wilson GR and Curry RW[4]; Demers LM, Spencer CA. *Laboratory Support for the Diagnosis and Monitoring of Thyroid Disease*. American Association for Clinical Chemistry; 2002. Available at www.aacc.org/members/nacb/Archive/LMPG/ThyroidDisease/Pages/ThyroidDiseasePDF.aspx. Accessed November 19, 2009; Supit EJ, Peiris AN. Interpretation of laboratory thyroid function tests for the primary care physician. *South Med J*. 2002;95:481-485.

Treatment:

The decision for treatment with levothyroxine should take into account the expense and inconvenience of daily medication, which is not acceptable to some patients, and the possibility of overdose with levothyroxine which can exacerbate osteoporosis or cause cardiac arrhythmias. Finally, the decision to treat depends on the careful consideration of the patient's clinical situation and preference.[18]

There are no universally accepted recommendations for the treatment of subclinical hypothyroidism. Recently published guidelines do not recommend routine treatment when TSH levels are below 10 mU/L. It is vital to confirm any elevation of TSH sustained over a three month period and then only treatment is given.[17]

Prevention:

By addition of iodine to the food hypothyroidism can be prevented in the large population. Endemic childhood hypothyroidism has become extinct due to the addition of iodine to the food. Not only by promoting eating of iodine rich food like dairy and fish the iodinisation of salt which is done is several countries has played a huge role in preventing hypothyroidism[54].

HYPERTHYROIDISM & THYROTOXICOSIS

Hyperthyroidism is one condition where excess amount of thyroid hormone is synthesized.Thyrotoxicosis is a clinical diagnosis due to tissue exposure to high levels of thyroid hormone in blood. Sometimes it may be arise due to over intake of hormone or ectopic site production.

The various forms of thyrotoxicosis are

1. DIFFUSE TOXIC GOITER (GRAVES' DISEASE)

Graves' disease is the most common form of thyrotoxicosis and may occur at any age, more commonly in females than in males. The syndrome consists of one or more of the following features: (1) thyrotoxicosis, (2) goiter, (3) ophthalmopathy (exophthalmos), and (4) dermopathy (pretibial myxedema).

ETIOLOGY

Graves' disease is an autoimmune disease of unknown etiology. Nowadays it is suggested there is more hereditary risk of developing disease is around 15%. Females to male ratio is 5: 1 in developing disease and mean age of presentation would be 20 t0 40 years.

PATHOGENESIS

In Graves' disease, T lymphocytes become activated to antigens in the thyroid gland and activate B lymphocytes to produce antibodies. One antibody is marked towards the TSH receptor site in the thyroid cell and has the ability to stimulate the thyroid cell to increased growth and function. The presence of this circulating antibody is positively correlated with active disease and with relapse of the disease. There is an strong hereditary predisposition, but still it's a question of debate which triggers acute reaction. There are various factors that may aggravate the immune response like ,(1) pregnancy, especially after delivery; (2) iodide deficient areas ; (3) treatment with lithium; (4)infections; and (5) glucocorticoid stoppage.

The mechanism of ophthalmopathy is due to cytotoxic lymphocytes and cytotoxic antibodies acts against to a antigen TSH-R present in orbital fibroblasts, orbital muscle, and thyroid tissue. Cytokines from these sensitized lymphocytes would cause inflammation of orbital fibroblasts and orbital myositis, resulting in enlarged orbital muscles, proptosis of the eye balls, and diplopia as well as redness, congestion, and conjunctival and periorbital edema.

The pathogenesis of thyroid dermopathy (pretibial myxedema) and the rare subperiosteal inflammation on the phalanges of the hands and feet (thyroid

osteopathy) it may also involve lymphocyte cytokine stimulation of fibroblasts in these locations.

CLINICAL FEATURES

SYMPTOMS AND SIGNS

In younger individuals, common manifestations include increased heart beat, anxiety, easy tiredness, increased movements, loose stools, increased sweating, heat intolerance, increased loss of weight with increase in loss of appetite. Swelling of gland, eye signs , and mild high heart rate may be seen. Muscle weakness and loss of muscle mass may be so severe that the patient cannot rise from a chair without assistance. In children, rapid growth with accelerated bone maturation occurs[46].

In patients over age 60, cardiovascular and myopathic manifestations predominate; the most common presenting complaints are palpitation, dyspnea on exertion, tremor, nervousness, and weight loss.

The eye signs of Graves' disease have been classified by Werner . This classification is useful in describing the extent of the eye involvement. The first letters of each class form the mnemonic “NO SPECS.”

- Class I involves upper lids spasm related with active thyrotoxicosis and subsides when thyrotoxicosis is controlled.
- Classes II-VI denote infiltrative disease involving orbital muscles and orbital tissues.
- Class II is associated with involvement of soft tissue with periorbital edema, congestion and edema of the conjunctiva.

- Class III is proptosis found by the Hertel exophthalmometer.
- Class IV consists of muscle involvement. The muscle most commonly involved in the infiltrative process is the inferior rectus, limiting upward gaze. Medial rectus is also affected so that lateral gaze is difficult.
- Class V is involvement of cornea.
- Class VI loss of vision from optic nerve involvement.

Thyroid ophthalmopathy is because of infiltration of muscles of orbit with lymphocytes and edema fluid formed because of inflammation. The orbit is a cone enclosed by bone, and swelling of the extraocular muscles within this closed space causing enlargement of the eyeball and restricted muscle movement, resulting in diplopia. Ocular muscle enlargement can be demonstrated by orbital CT scanning or MRI. When muscle swelling occurs posteriorly, toward the apex of the orbital cone, the optic nerve is compressed, which may cause loss of vision.

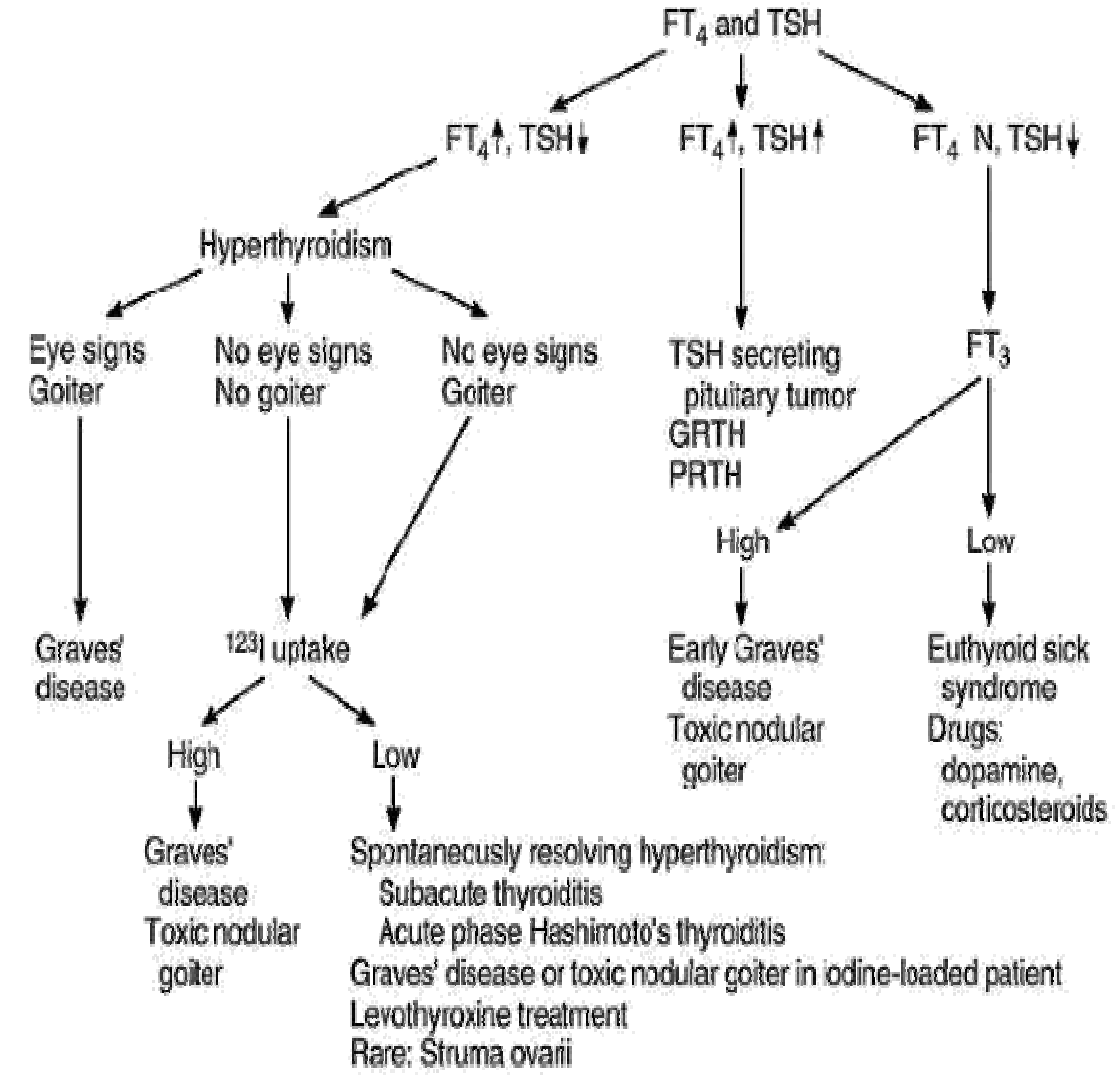
LABORATORY FINDINGS

Essentially, the combination of an increased free thyroxine T4 and a decreased Thyroid stimulating hormone makes the diagnosis of hyperthyroidism. Ophthal signs are there, the diagnosis of Graves' disease is confirmed. Otherwise if absent, patient should undergo radioiodine uptake even in absence of goiter. Increased uptake is conclusive of Graves' disease or toxic nodular goiter. Decreased uptake is present in other hyperthyroid which is benign and thyroiditis[22]. It can also be present in thyroxine treatment overload. Or, rarely, in association with a struma ovarii. If both FT_4 and TSH are elevated and radioiodine uptake is also elevated, consider a TSH-secreting pituitary tumor or generalized or pituitary resistance syndromes. If FT_4 is normal and TSH is suppressed, check FT_3, which will be elevated in early Graves' disease or in T_3-secreting toxic nodules. Low FT_3 will be found in the euthyroid sick syndrome or in patients receiving corticoids or dopamine.

Thyroid autoantibodies Tg Ab and TPO Ab are usually present in both Graves' disease and Hashimoto's thyroiditis, but TSH-R Ab is specific for Graves' disease. The ^{123}I or technetium scan is useful to evaluate the size of the gland or the presence of “hot” or “cold” nodules. CT and MRI scans of the orbit have reveales muscle enlargement in most patients with Graves' disease even when there is no clinical evidence of ophthalmopathy.

DIFFERENTIAL DIAGNOSIS

Graves' disease wont present in its usual manner. It can present with unlikely form where diagnosing is difficult. significant muscle wasting signifies severe myopathy. Thyrotoxic periodic paralysis is rare form and will have a sudden attack of flaccid paralysis and hypokalemia. The paralysis subsides naturally and can be prevented by potassium treatment and beta blockers. The illness is cured by appropriate treatment of the thyrotoxicosis. Patients with thyrocardiac disease present primarily with symptoms of heart involvement especially refractory atrial fibrillation insensitive to digoxin or with high-output heart failure. Half the number of patients have no previous heart problems and are reversed once treated thyrotoxicosis[26]. In few aged patients will present with loss of weight , tiny goiter , decreased atrial fibrillation, and severe depression, with no evidence increased catecholamine reactivity. These placid patients have “apathetic hyperthyroidism.” Finally, some young women may present with amenorrhea or infertility as the primary symptom. In all of these instances, the diagnosis of hyperthyroidism can usually be made on the basis of the clinical and laboratory studies.



LABORATORY TESTS FOR DIAGNOSIS OF HYPERTHYROIDISM

TREATMENT OF GRAVES' DISEASE

Three modes of treatment

(1) antithyroid drug therapy

(2) surgery

(3) radioactive iodine therapy.

A. ANTITHYROID DRUG THERAPY

In general, antithyroid drug therapy is most useful in young patients with small glands and mild disease. The drugs propylthiouracil or methimazole are given until the disease undergoes spontaneous remission.Treatment period varies fromed for 6 months to 15 years. This mode of treatment has increased relapse rate. Antithyroid drugs usually started in high doses till patient becomes euthyroid, then maintenance therapy achieved. A common regimen consists of giving propylthiouracil, 100 mg every 6 hours initially, and then in 4–8 weeks reducing the dose to 50–200 mg once or twice daily. Propylthiouracil has one advantage over methimazole by inhibiting the T4 conversion to T3. Me-thimazole has a longer duration of action and is more useful if a single daily dose is desirable. FT4 and TSH are used in assessment of treatment.

An alternative method of therapy is combination of methimazole with levothyroxine to prevent hypothyroidism.

Duration of therapy—The duration of therapy with antithyroid drugs in Graves' disease ranges from 6 months to 20 years . A sustained remission may be predicted in about 80% of treated patients in the following circumstances: (1) if the thyroid gland reverts to normal size; (2) if the disease can be suppressed with little dose of antithyroid drugs; (3) TSH-R Ab is should be no longer detectable in the serum.

A. SURGICAL TREATMENT

For large glands and MNG , subtotal thyroidectomy is done. The patient should be made euthyroid before surgery. Potassium iodide given before two weeks of surgery to reduce vascularity. There is still a debate in leaving how much thyroid tissue back. Most of them need postop thyroxine supplementation. Complications like nerve injury can occur[22].

C. RADIOACTIVE IODINE THERAPY

In old aged patients and in whom preexisting heart disease or other medical problems, severe thyrotoxicosis, ideal thing is to attain euthyroid state before therapy. For this , pretreatment with methimazole is given . Because it is usually desirable to destroy most of the gland in patients with underlying medical problems, the dose of ^{131}I may be slightly larger than is ordinarily given.

Major adverse effect of this therapy is hypothyroidism and it will be present in 80% of cases. They can be treated with thyroxine replacement therapy. Hypothyroidism

may occur after any type of therapy for Graves' disease even after antithyroid drug therapy; in some patients, “burned-out” Graves' disease may be an end result of autoimmune thyroid disease. Accordingly all patients with Graves' disease require lifetime follow-up to be certain that they remain euthyroid.

NERVE CONDUCTION STUDY:

Principles of motor conduction study:

- Normally a motor or mixed nerve is stimulated in two points along its course.it generates a pulse,and it is adjusted to record CMAP.
- By keeping the cathode close to the active recording electrode site,a suprmaximal stimulus is generated. And it is necessary that this supramaximal stimulus is needed to record the CMAP in order to avoid hyperpolarisation effect and anode conduction block.
- Surface recording electrode is commonly used for recording.and usually it s placed in belly tendon montage.
- The active electrode is placed in the reference point in such a way that it is close to motor point and ground electrode is placed in between stimulating and recording electrode.
- Normally it will show a biphasic action potential with initial negativity.
- A square wave pulse of 0.1 ms duration with intensity of 5 -40 ms is needed for surface stimulation of healthy nerve.

- The nerve excitability is normally decreased in diseased nerve.so that the requirement of current is normally higher than the healthy one.
- The measurement of the motor nerve include latency,duration of CMAP, amplitude of CMAP,and nerve conduction velocity.

Onset latency:

- Time duration between the stimulus artefact to the initial negative deflection of CMAP, which is measured in milli seconds.
- It is a measure of conduction.it also includes the propagation time along the muscle and neuromuscular transmission time.

Amplitude of CMAP:

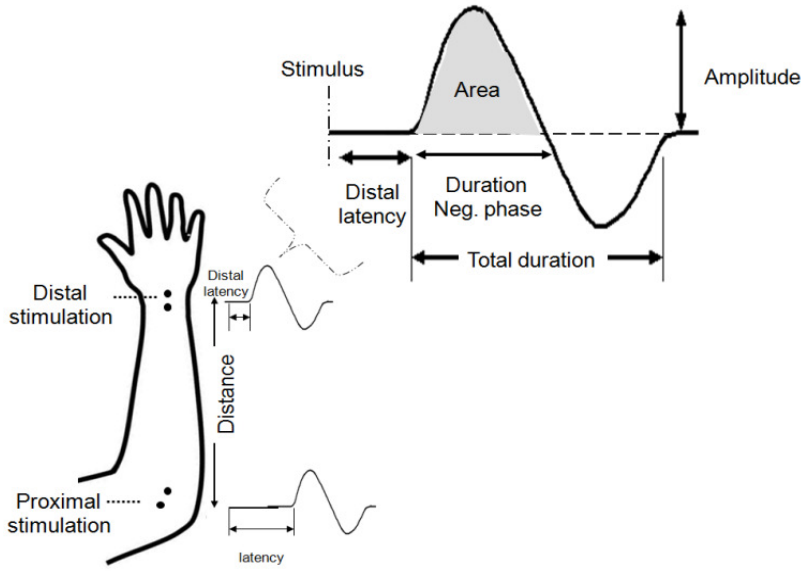
- It is measured in two ways. Base –peak method and peak –peak method.
- It implies the number of nerve fibres.

Duration of CMAP:

- It is measured from the onset to the negative or positive peak or the final return to baseline of the wave.
- It correlates with the density of the nerve fibres.

Motor nerve conduction velocity:

- It is calculated by dividing the distance between the two points of stimulation with the latency difference.it is expressd in m/s.the distance between the two points must be atleast 10 cm.
- In the evaluation of focal compressive neuropathies like CTS, stimulation of shorter segments of the nerve is necessary.



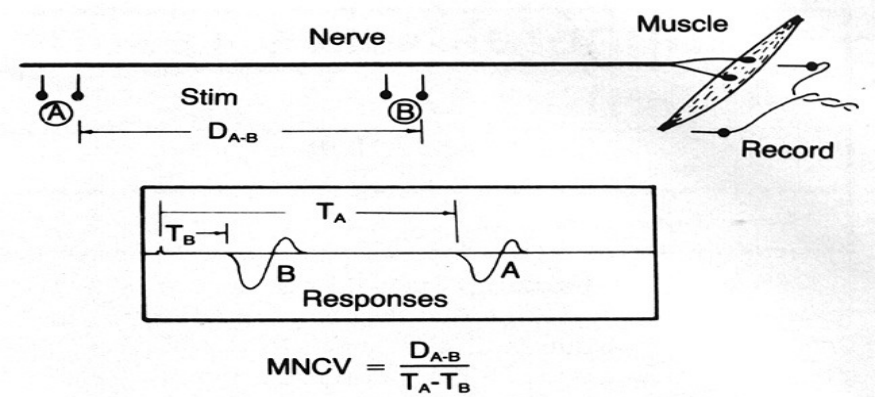


FIG. D-2 Schematic diagram of motor nerve conduction velocity (MNCV) estimation. The nerve is stimulated at two sites, and recording is done from the muscle.

Principles of sensory nerve conduction study:

By the following two methods it can be measured.

1) Orthodromic conduction
2) Antidromic conduction

Orthodromic conduction:

- Distal portion of the nerve is stimulated and SNAP is recorded proximally along the nerve.

Antidromic conduction:

- The nerve is stimulated in the proximal region of the nerve and SNAP is recoded from the distal site.
- Ring electrodes are preferred to stimulate the digital nerves in case of orthodromic stimulation.where as surface electrodes are used for antidromic stimulation.

- Filter settings: 10 Hz to 2 kHz,sweep speed 1-2 ms/division and gain 1-5uV/division.
- The sensory nerve conduction measurement also includes onset, latency, amplitude, duration of SNAP, and nerve conduction velocity.

Latency of sensory nerve:

- The latency for orthodromic stimulation is measured from the stimulus artifact to the initial positive or subsequent negative peak.
- In case of antidromic stimulation latency is larger compared with orthodromic stimulation.

Amplitude of SNAP:

- Triphasic appearance because of the initial positive peak in SNAP is a classic feature of orthodromic potential.the initial positivity is lacking in case of antidromic potential.
- It's measured from base line to negative peak or from positive to negative peak.The amplitude suggests that the density of the nerve fibers.

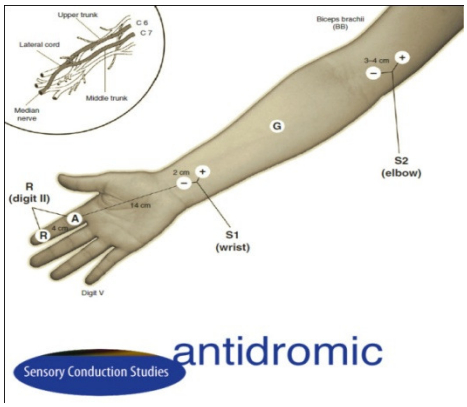
Duration of SNAP:

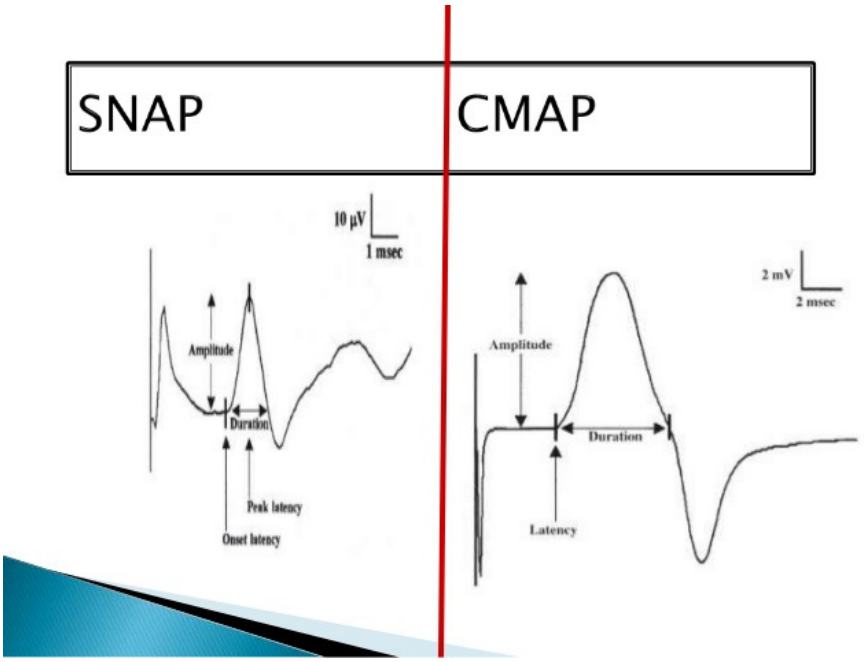
- It is measured from the initial positive peak to the intersection between the descending phase and the baseline or to the negative or subsequent positive peak or return to the baseline.

- the duration denotes the number of slow conducting fibers.

Sensory motor conduction velocity:

- it is measured by dividing the distance between the stimulating and recording sites by the latency.
- Compared with SNAP amplitude, CMAP amplitude remain stable or there is little change on proximal stimulation.





Variables affecting nerve conduction study

- Physiological

  1)age

  2)temperature

  3)upper vs lower limb

- Technical

  1)stimulation:

  - Faulty location of stimulator
  - Fat or edma between stimulator and nerve
  - Bridge formation between anode and cathode

2)Recording

- Break in cable
- Wrongly connected preamplifier
- Wrong settings of gain,sweep,filter, and incorrect position of active and reference electrode

3)inadvertent stimulation on unwanted nerve

- Volume conduction
- Anomalous innervations

AIMS & OBJECTIVES:

To Study the Nerve Conduction Abnormalities In Patients With newly detected Thyroid Dysfunction

PLACE OF STUDY:

Medicine OPD and Endocrinology OPD at Stanley Medical College and Hospital

STUDY POPULATION

50 patients with newly detected thyroid dysfunction including both hypothyroidism and hyperthyroidism.

STUDY PERIOD : Feb 2015 to Sep 2015

STUDY DESIGN: Descriptive Study

CASE DEFINITION:

Patients with newly detected thyroid dysfunction including both hypothyroidism and hyperthyroidism according to the following table

Thyroid functional state	TSH (0.3–3.3 mU/L)	Free T_4 (10–30 nmol/L)	Free T_3 (3.5–7.5 µmol/L)
EUTHYROID	Normal	Normal	Normal
HYPERTHYROID	Undetectable	High	High
HYPOTHYROID	High	Low	Low

INCLUSION CRITERIA:

Patients aged between 20-60 yrs with newly detected thyroid dysfunction including both hypothyroidism and hyperthyroidism

EXCLUSION CRITERIA:

- Patients takings ANTI CANCER MEDICATION, ANTI HIV MEDICATION, METRONIDAZOLE and other drugs causing neuropathy etc..
- Patients with CHRONIC ALCHOLISM
- Patients with DIABETES MELLITUS
- Patients those who are pregnant
- Patients those who are kept in INTENSIVE CARE UNITS.
- Patients with other co-morbid illness that would predispose to neuropathy like connective tissue disorders, liver failure, kidney failure.etc..

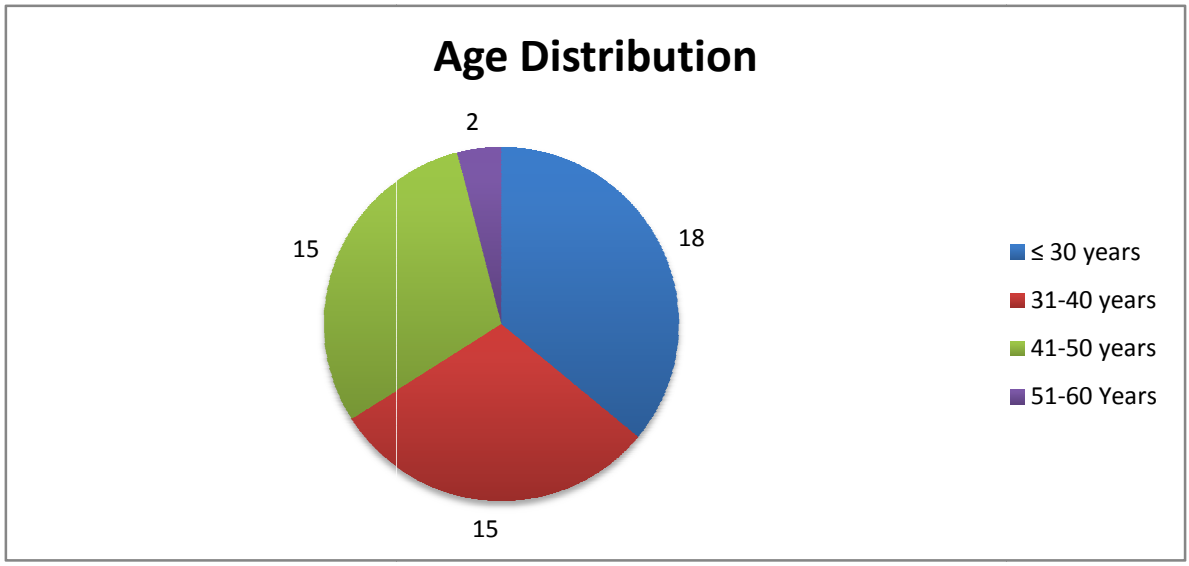
MATERIALS AND METHODS

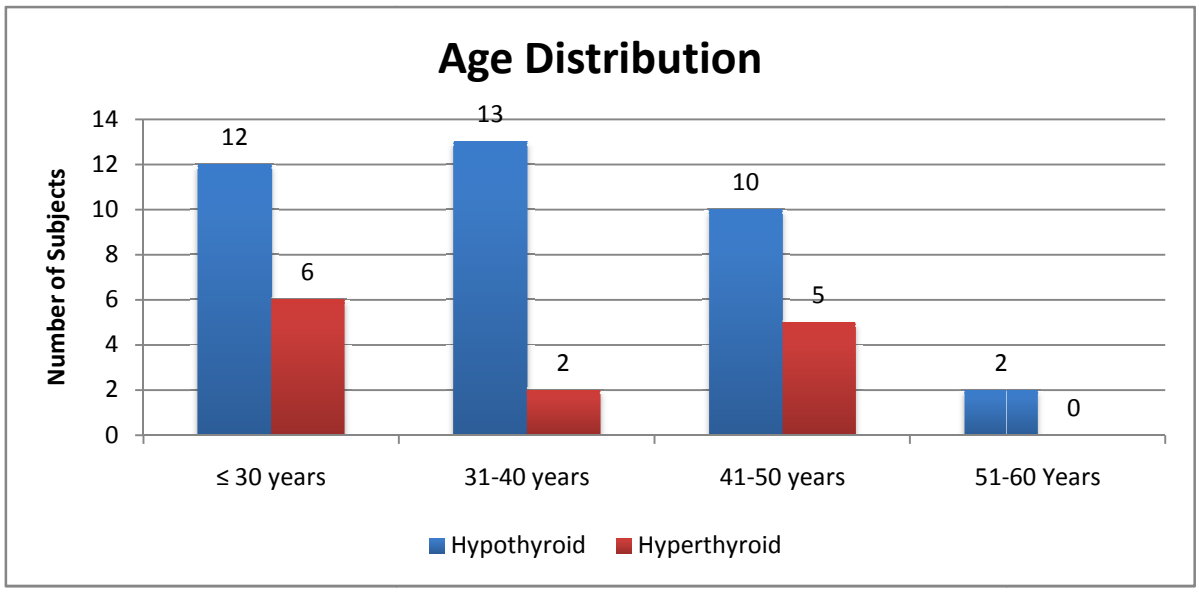
50 Patients with newly detected thyroid dysfunction, those who attended Medicine OPD, endocrinology OPD at Stanley medical college hospital, Chennai were included in this study. The data were recorded from each subject with an in-person interview by administering a specific questionnaire. Nerve Conduction Study were performed by using the Standard RMS ENMG EP MARK II machine in all adult patients with thyroid dysfunction. The Latency, Amplitude, duration, area and velocity of motor and sensory nerves will be studied. Three surface disc electrodes, Recording electrode, Reference electrode and Ground electrode were placed after applying jelly to reduce resistance in air between electrode and skin surface. MNCV were evaluated by Belly Tendon montage. SNCV was measured by anti-dromic stimulation

RESULTS AND DISCUSSION

Descriptive statistics was done for all data and were reported in terms of mean values and percentages. Suitable statistical tests of comparison were done. Continuous variables were analysed with the unpaired t test.. Categorical variables were analysed with the Chi-Square Test and Fisher Exact Test. Statistical significance was taken as $P < 0.05$. The data was analysed using SPSS version 16 and Microsoft Excel 2007.

AGE





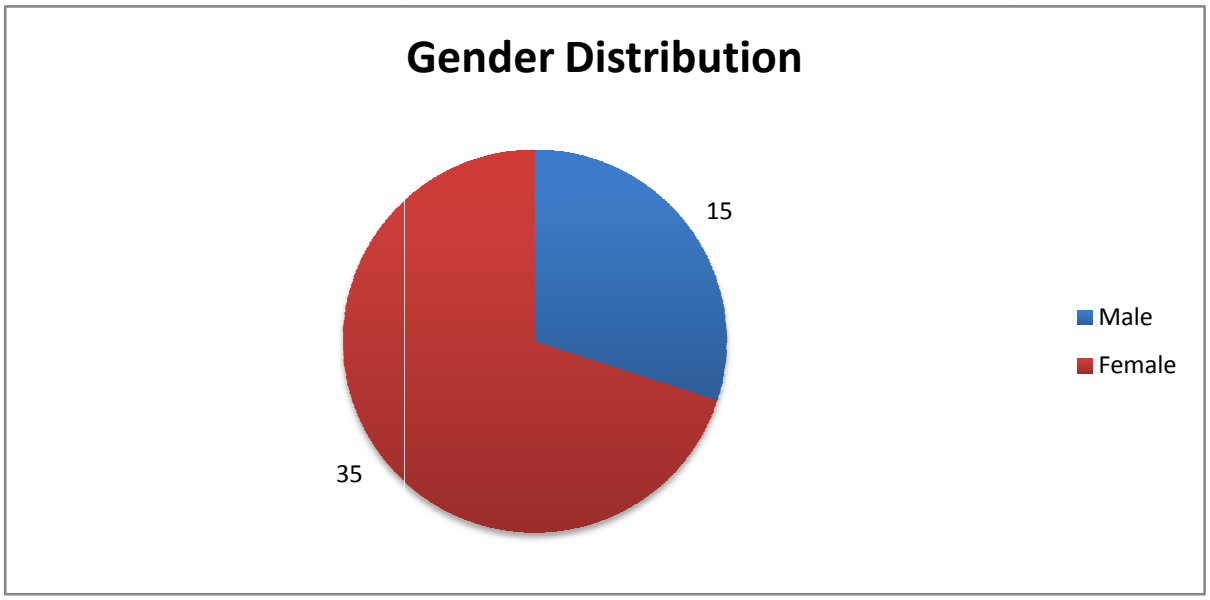
Age Distribution	All	%	Hypothyroid	%	Hyperthyroid	%
≤ 30 years	18	36.00	12	32.43	6	46.15
31-40 years	15	30.00	13	35.14	2	15.38
41-50 years	15	30.00	10	27.03	5	38.46
51-60 Years	2	4.00	2	5.41	0	0.00

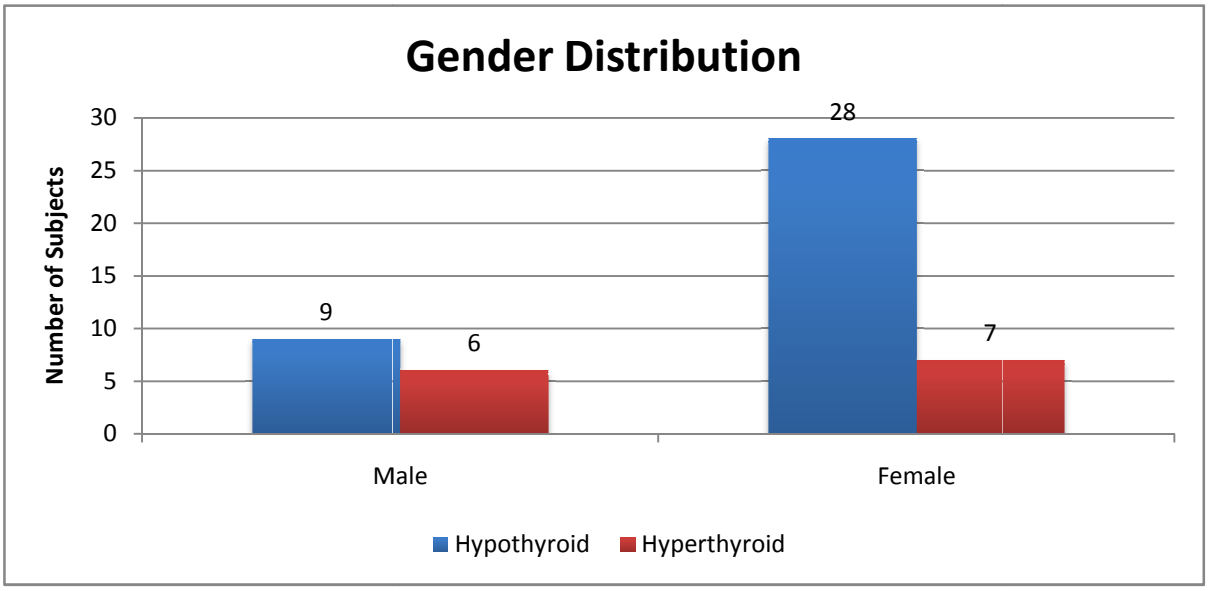
Total	50	100	37	100	13	100

Age Distribution	All	Hypothyroid	Hyperthyroid
N	50	37	13
Mean	35.14	35.27	34.77
SD	9.45	9.11	10.73
P value Unpaired t Test			0.8820

Majority of the hypothyroid Group patients belonged to the 31-40 years age class interval (n=13, 35.14%) with a mean age of 35.37 years. In the hyperthyroid group patients, majority belonged to the ≤ 30 years age class interval (n=6, 46.15%) with a mean age of 34.77 years. The association between the intervention groups and age distribution is considered to be not statistically significant since $p > 0.05$ as per unpaired t test.

GENDER

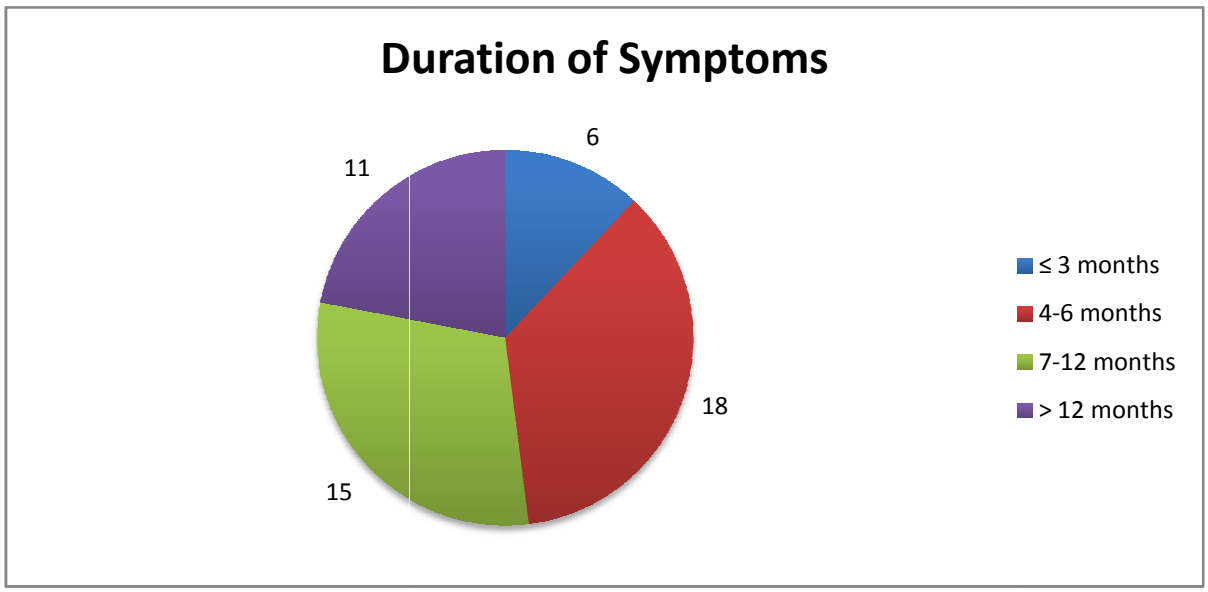


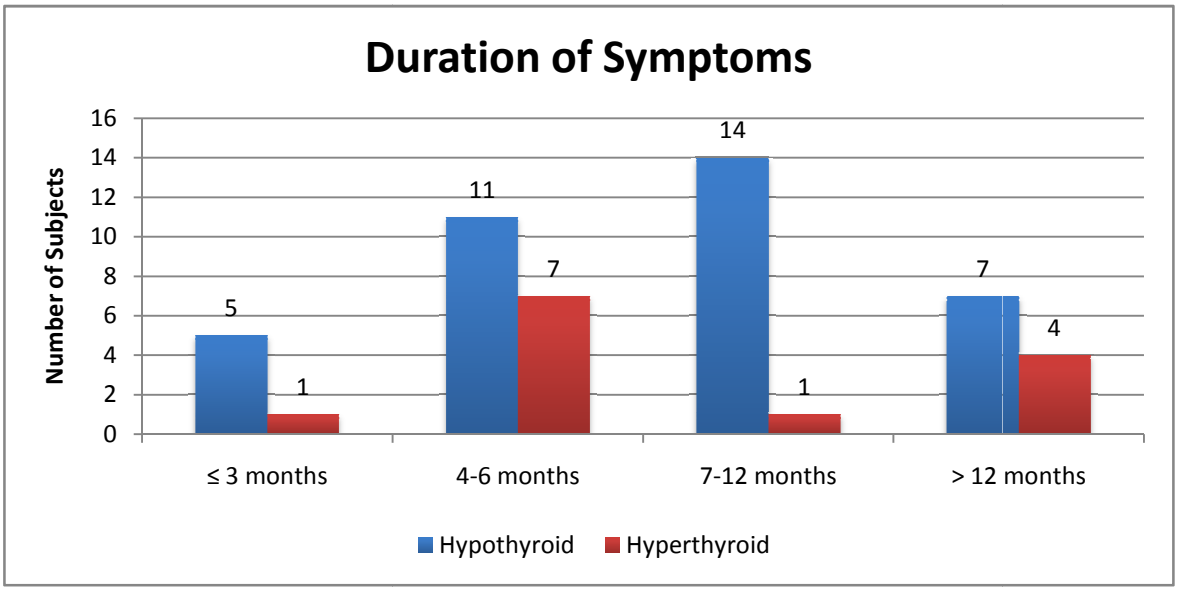


Gender Distribution	All	%	Hypothyroid	%	Hyperthyroid	%
Male	15	30.00	9	24.32	6	46.15
Female	35	70.00	28	75.68	7	53.85
Total	50	100	37	100	13	100
P value Fishers Exact Test			0.1704			

Majority of the hypothyroid Group patients belonged to the female gender class interval (n=28, 75.68. In the hyperthyroid group patients, majority belonged to the female gender class interval (n=7, 53.85%) . The association between the study groups and gender distribution is considered to be not statistically significant since $p > 0.05$ as per fishers exact test.

DURATION OF SYMPTOMS

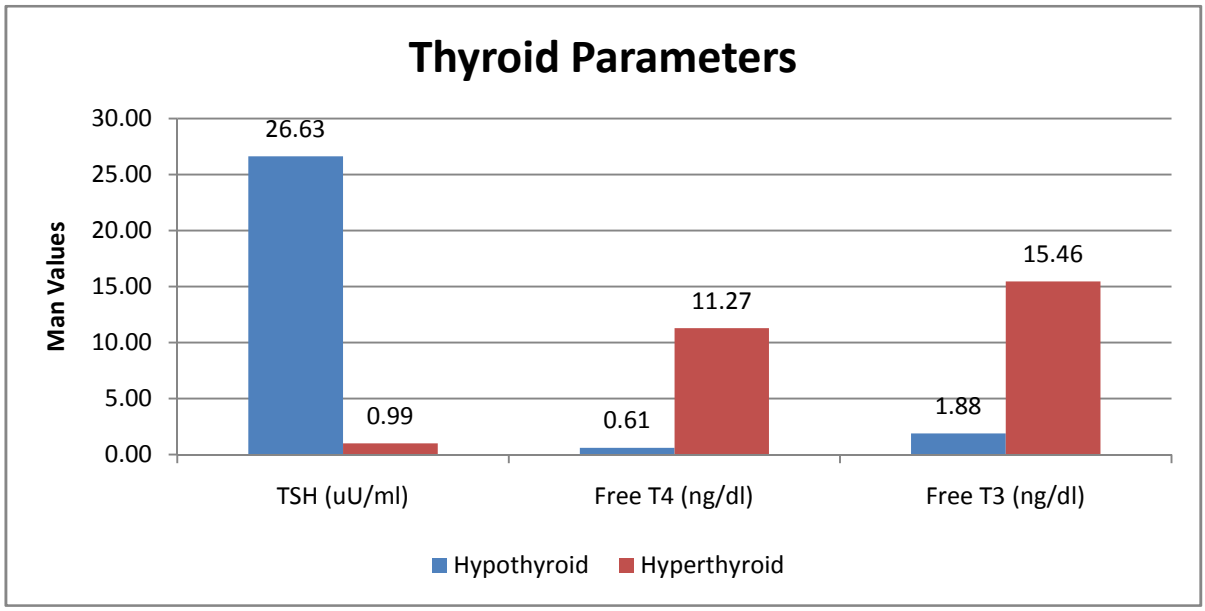




Duration of Symptoms	All	%	Hypothyroid	%	Hyperthyroid	%
≤ 3 months	6	12.00	5	13.51	1	7.69
4-6 months	18	36.00	11	29.73	7	53.85
7-12 months	15	30.00	14	37.84	1	7.69
> 12 months	11	22.00	7	18.92	4	30.77
Total	50	100	37	100	13	100
P value Fishers Exact Test			0.9851			

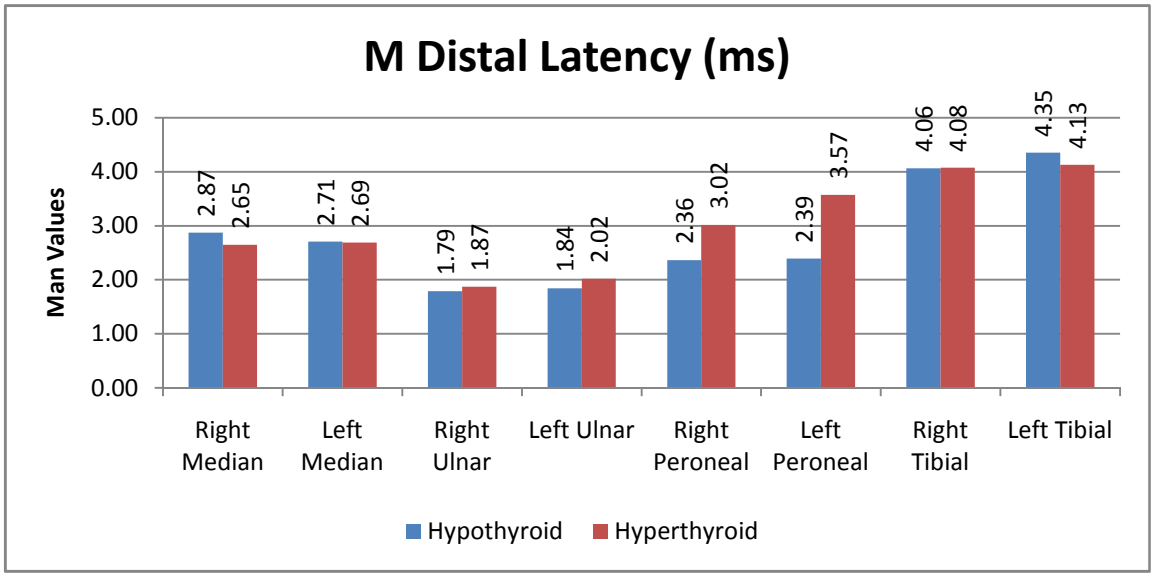
Majority of the hypothyroid Group patients belonged to the 7-12 months duration of symptoms class interval (n=14, 37.84). In the hyperthyroid group patients, majority belonged to the 4-6 months duration of symptoms class interval (n=7, 53.85%) . The association between the study groups and duration of symptoms is considered to be not statistically significant since $p > 0.05$ as per fishers exact test.

THYROID PARAMETERS



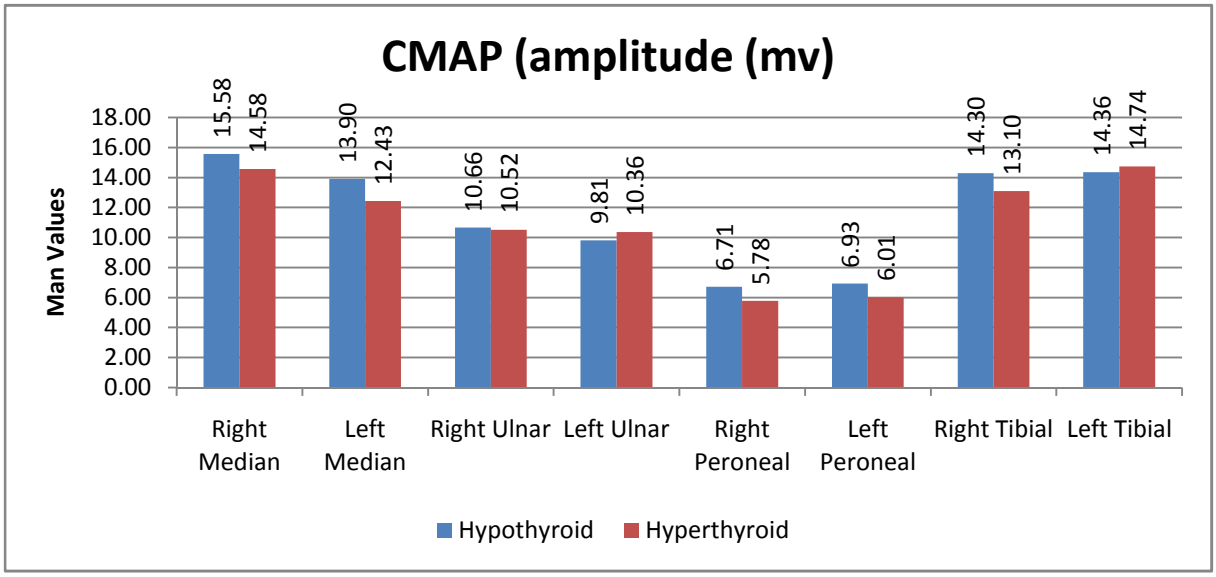
Thyroid Parameters		TSH (uU/ml)	Free T4 (ng/dl)	Free T3 (ng/dl)
All	N	50	50	50
	Mean	19.96	3.39	5.41
	SD	26.05	5.58	6.98
Hypothyroid	N	37	37	37
	Mean	26.63	0.61	1.88
	SD	27.31	0.22	0.50
Hyperthyroid	N	13	13	13
	Mean	0.99	11.27	15.46
	SD	2.69	5.99	7.12

M DISTAL LATENCY (ms)



M Distal Latency (ms)		Right Median	Left Median	Right Ulnar	Left Ulnar	Right Peroneal	Left Peroneal	Right Tibial	Left Tibial
All	N	50	50	50	50	50	50	50	50
	Mean	2.81	2.70	1.81	1.89	2.53	2.70	4.07	4.29
	SD	0.60	0.64	0.59	0.56	0.85	0.98	0.51	0.59
Hypothyroid	N	37	37	37	37	37	37	37	37
	Mean	2.87	2.71	1.79	1.84	2.36	2.39	4.06	4.35
	SD	0.68	0.71	0.61	0.58	0.74	0.84	0.50	0.60
Hyperthyroid	N	13	13	13	13	13	13	13	13
	Mean	2.65	2.69	1.87	2.02	3.02	3.57	4.08	4.13
	SD	0.26	0.41	0.55	0.47	0.99	0.80	0.55	0.56
P value Unpaired t Test		0.1001	0.9118	0.6554	0.2836	0.2449	0.1123	0.9412	0.2347

CMAP (amplitude (mv)



CMAP (amplitude (mv)		Right Median	Left Median	Right Ulnar	Left Ulnar	Right Peroneal	Left Peroneal	Right Tibial	Left Tibial
All	N	50	50	50	50	50	50	50	50
	Mean	15.32	13.52	10.62	9.95	6.47	6.69	13.99	14.46
	SD	11.50	4.57	2.46	2.31	2.32	2.14	5.34	5.11
Hypothyroid	N	37	37	37	37	37	37	37	37
	Mean	15.58	13.90	10.66	9.81	6.71	6.93	14.30	14.36
	SD	12.94	4.58	2.37	2.30	2.44	1.98	5.62	5.25
Hyperthyroid	N	13	13	13	13	13	13	13	13
	Mean	14.58	12.43	10.52	10.36	5.78	6.01	13.10	14.74
	SD	5.08	3.52	2.42	2.08	1.42	2.12	4.12	4.48
P value Unpaired t Test		0.0140	0.0253	0.0168	0.0411	0.0027	0.0479	0.0493	0.0169

Mean CMAP (amplitude (mv))	Hypothyroid	Hyperthyroid	Overall
Median	14.74	13.50	14.12
Ulnar	10.44	10.23	10.34
Peroneal	6.82	5.90	6.36
Tibial	14.33	13.92	14.13

Results

In patients belonging to hypothyroid Group, the mean CMAP- median is 14.74 mv, CMAP – ulnar is 10.23 mv, CMAP – peroneal is 6.82 mv and CMAP – tibial is 14.33 mv. Similarly in hyperthyroid patients CMAP- median is 13.50 mv, CMAP – ulnar is 10.44 mv, CMAP – peroneal is 5.90 mv and CMAP – tibial is 13.92 mv. . The increased mean CMAP measurements overall and in hypothyroid group compared to the hyperthyroid Group is statistically significant as the p value is < 0.05 as per unpaired t-test indicating a true difference among study groups.

Discussion

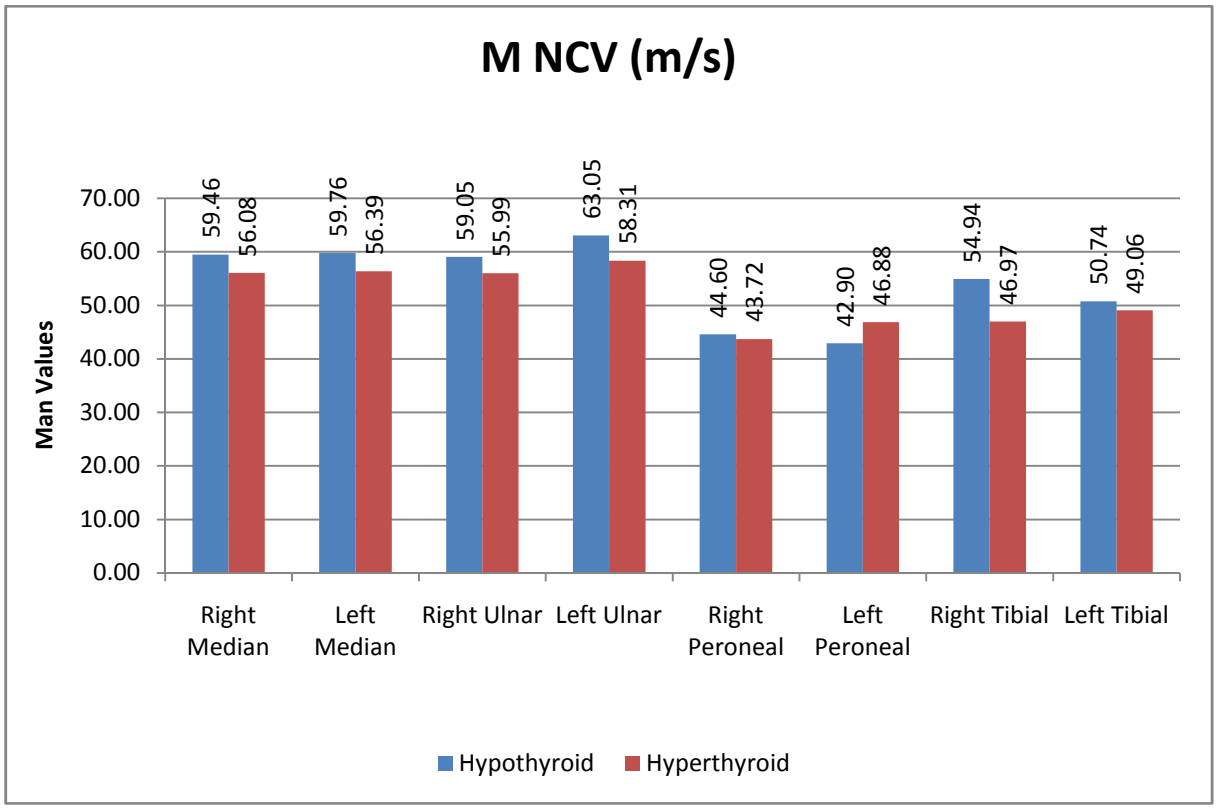
The mean CMAP measurements were meaningfully more overall and especially in Hypothyroid Group compared to the hyperthyroid Group. This significant difference of increased mean CMAP (mean difference – Median(1.24 mv, 9%), Ulnar(0.21 mv, 2%), Peroneal(0.92 mv, 16%) and Tibial(0.41 mv, 3%), measurement in Hypothyroid Group compared to the hyperthyroid Group is true and has not occurred by chance.

Conclusion

In this study we can safely conclude that mean CMAP measurements were

significantly and consistently higher overall and especially in Hypothyroid Group compared to the hyperthyroid Group

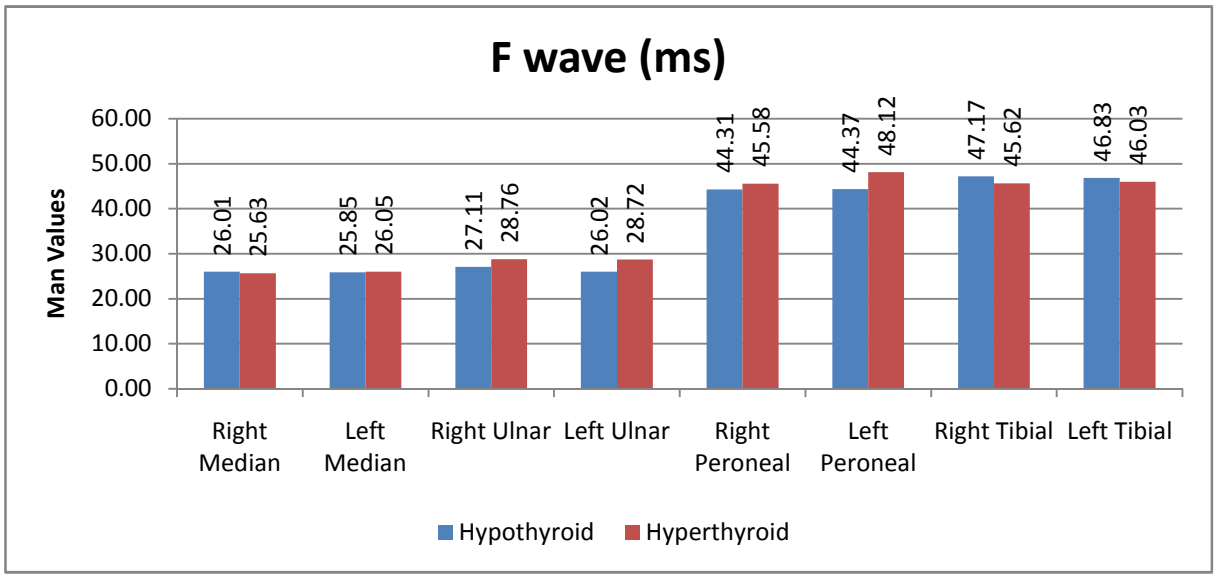
M NCV (m/s)



M NCV (m/s)		Right Median	Left Median	Right Ulnar	Left Ulnar	Right Peroneal	Left Peroneal	Right Tibial	Left Tibial
All	N	50	50	50	50	50	50	50	50
	Mean	58.58	58.88	58.25	61.82	44.38	43.93	52.87	50.30
	SD	5.86	6.02	5.56	7.14	4.28	6.86	23.07	10.76
Hypothyroid	N	37	37	37	37	37	37	37	37
	Mean	59.46	59.76	59.05	63.05	44.60	42.90	54.94	50.74
	SD	6.16	6.47	5.17	7.61	4.41	7.44	26.42	12.16
Hyperthyroid	N	13	13	13	13	13	13	13	13
	Mean	56.08	56.39	55.99	58.31	43.72	46.88	46.97	49.06
	SD	4.17	3.67	6.22	4.08	3.99	3.68	5.33	5.18
P value Unpaired t Test		0.1354	0.2277	0.1288	0.3378	0.5122	0.4162	0.0896	0.5002

By conventional criteria the association between the study groups and M NCV values distribution is considered to be not statistically significant since $p > 0.05$

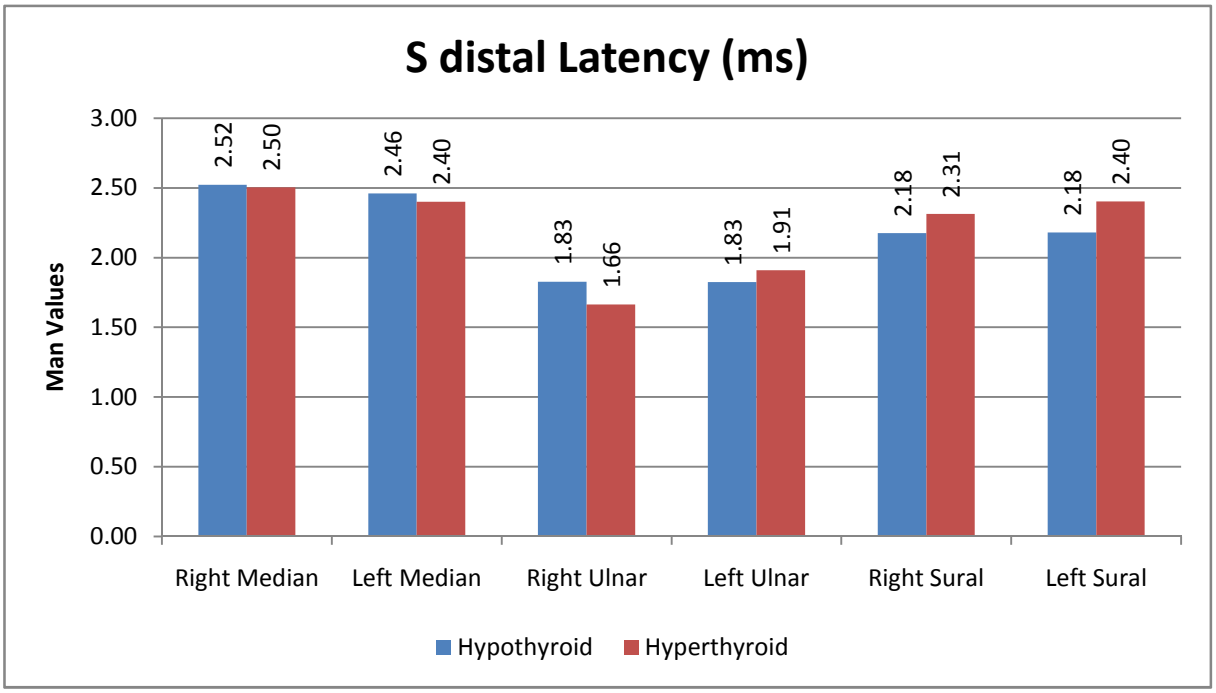
F WAVE (MS)


F wave (ms)
Man Values
60.00
50.00
40.00
30.00
20.00
10.00
0.00
26.01
25.63
25.85
26.05
27.11
28.76
26.02
28.72
44.31
45.58
44.37
48.12
47.17
45.62
46.83
46.03
Right Median
Left Median
Right Ulnar
Left Ulnar
Right Peroneal
Left Peroneal
Right Tibial
Left Tibial
Hypothyroid
Hyperthyroid

F wave (ms)		Right Median	Left Median	Right Ulnar	Left Ulnar	Right Peroneal	Left Peroneal	Right Tibial	Left Tibial
All	N	50	50	50	50	50	50	50	50
	Mean	25.91	25.91	27.54	26.72	44.64	45.34	46.77	46.62
	SD	1.95	1.72	4.00	4.26	4.77	4.23	4.18	3.92
Hypothyroid	N	37	37	37	37	37	37	37	37
	Mean	26.01	25.85	27.11	26.02	44.31	44.37	47.17	46.83
	SD	2.01	1.83	2.25	2.22	5.11	3.82	3.08	2.67
Hyperthyroid	N	13	13	13	13	13	13	13	13
	Mean	25.63	26.05	28.76	28.72	45.58	48.12	45.62	46.03
	SD	1.81	1.38	6.94	7.31	3.63	4.24	6.39	6.40
P value Unpaired t Test		0.5296	0.6856	0.4155	0.2130	0.3389	0.5110	0.4120	0.6688

By conventional criteria the association between the study groups and F wave values distribution is considered to be not statistically significant since $p > 0.05$

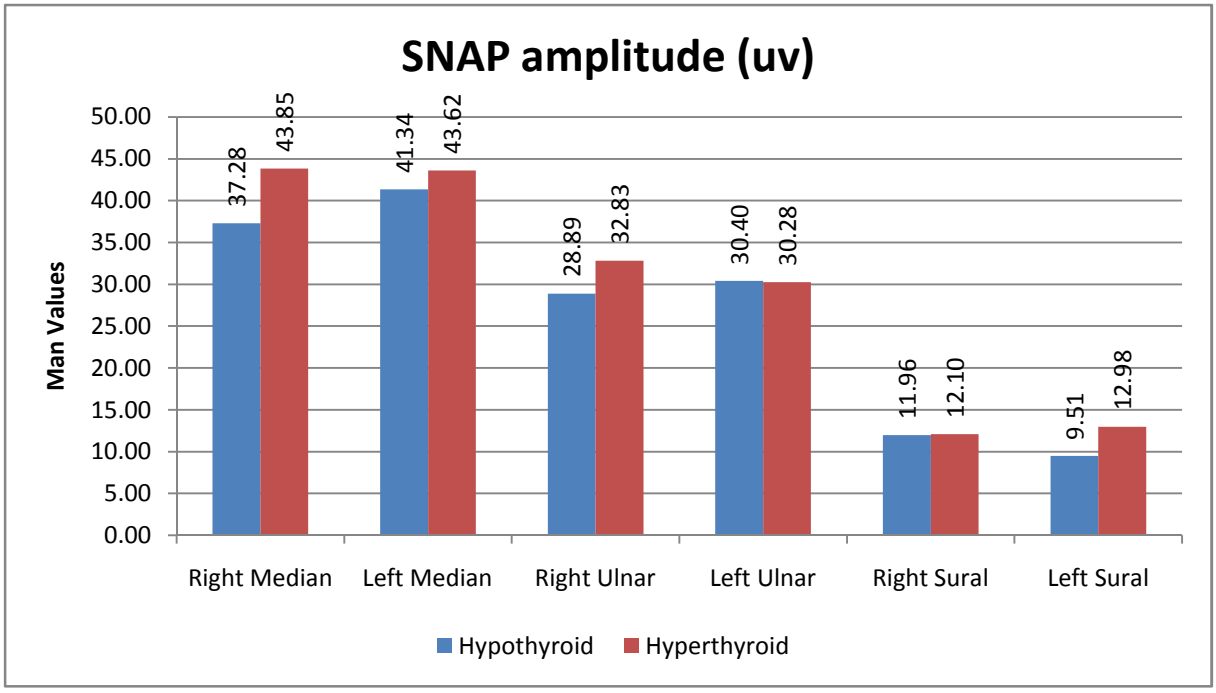
S DISTAL LATENCY (MS)



S distal Latency (ms)		Right Median	Left Median	Right Ulnar	Left Ulnar	Right Sural	Left Sural
All	N	50	50	50	50	50	50
	Mean	2.52	2.45	1.78	1.85	2.21	2.24
	SD	0.37	0.37	0.30	0.29	0.55	0.62
Hypothyroid	N	37	37	37	37	37	37
	Mean	2.52	2.46	1.83	1.83	2.18	2.18
	SD	0.38	0.39	0.28	0.28	0.54	0.60
Hyperthyroid	N	13	13	13	13	13	13
	Mean	2.50	2.40	1.66	1.91	2.31	2.40
	SD	0.36	0.29	0.33	0.32	0.60	0.67
P value Unpaired t Test		0.8692	0.5633	0.1334	0.4103	0.4718	0.3031

By conventional criteria the association between the study groups and S distal Latency values distribution is considered to be not statistically significant since $p > 0.05$

SNAP AMPLITUDE (UV)



SNAP amplitude (uv)		Right Median	Left Median	Right Ulnar	Left Ulnar	Right Sural	Left Sural
All	N	50	50	50	50	50	50
	Mean	38.99	41.93	29.92	30.37	11.99	10.41
	SD	19.89	21.25	24.86	15.98	8.81	7.59
Hypothyroid	N	37	37	37	37	37	37
	Mean	37.28	41.34	28.89	30.40	11.96	9.51
	SD	18.41	21.55	19.32	13.73	9.15	6.56
Hyperthyroid	N	13	13	13	13	13	13
	Mean	43.85	43.62	32.83	30.28	12.10	12.98
	SD	22.75	20.14	36.29	20.84	7.04	9.43
P value Unpaired t Test		0.0370	0.0420	0.0213	0.0147	0.0046	0.0226

SNAP amplitude (uv)	Hypothyroid	Hyperthyroid	Overall
Median	39.31	43.74	41.52
Ulnar	29.65	31.55	30.60
Sural	10.73	12.54	11.64

Results

In patients belonging to hypothyroid Group, the mean SNAP- median is 39.31uv, SNAP – ulnar is 29.65uv and SNAP – suralis 10.73uv. Similarly in hyperthyroid patients SNAP - median is 43.74 uv., SNAP – ulnar is 31.55 uv. and SNAP –sural is 12.54 uv.. . The increased mean SNAP measurements overall and decreased in hypothyroid group compared to the hyperthyroid Group is statistically significant as the p value is < 0.05 as per unpaired t- test indicating a true difference among study groups.

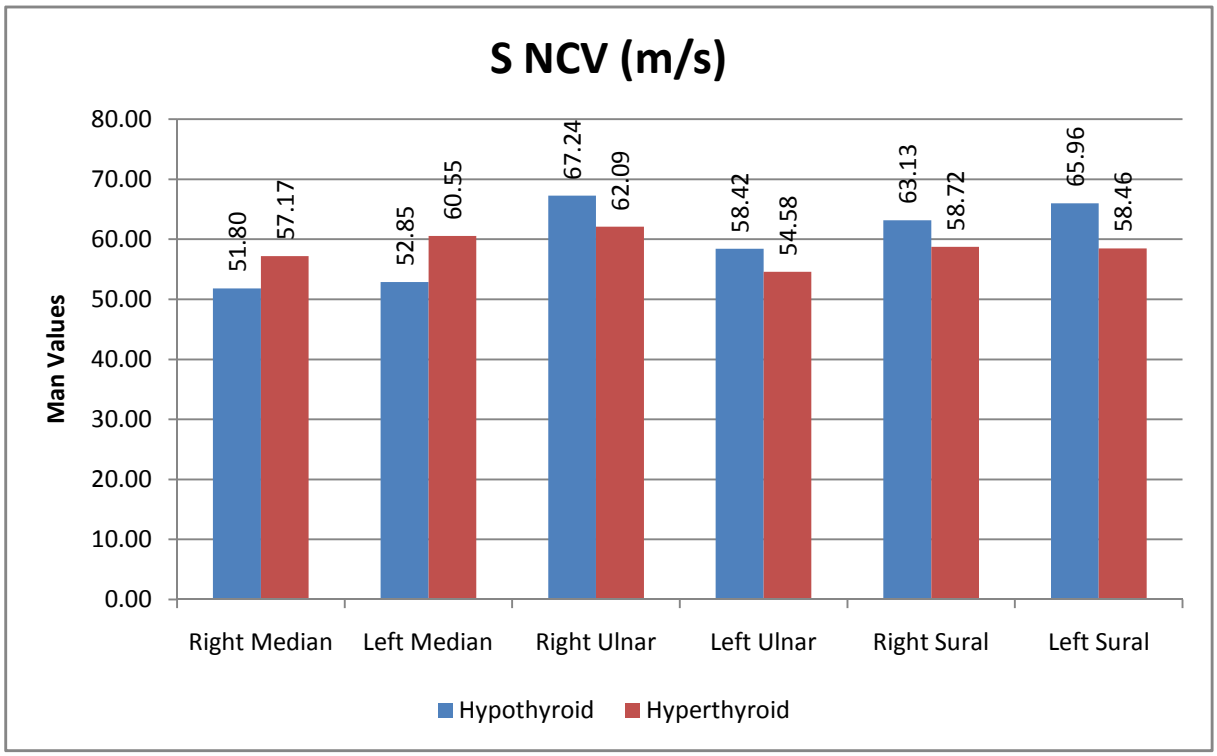
Discussion

The mean SNAP measurements were meaningfully more overall and less in Hypothyroid Group compared to the hyperthyroid Group. This significant difference of decreased mean SNAP (mean difference – Median(4.43 nv, 10%), Ulnar(1.91 mv,6%) and Sural(1.81 mv, 14%), measurement in Hypothyroid Group compared to the hyperthyroid Group is true and has not occurred by chance.

Conclusion

In this study we can safely conclude that mean SNAP measurements were significantly and consistently higher overall and especially lowered in Hypothyroid Group compared to the hyperthyroid Group

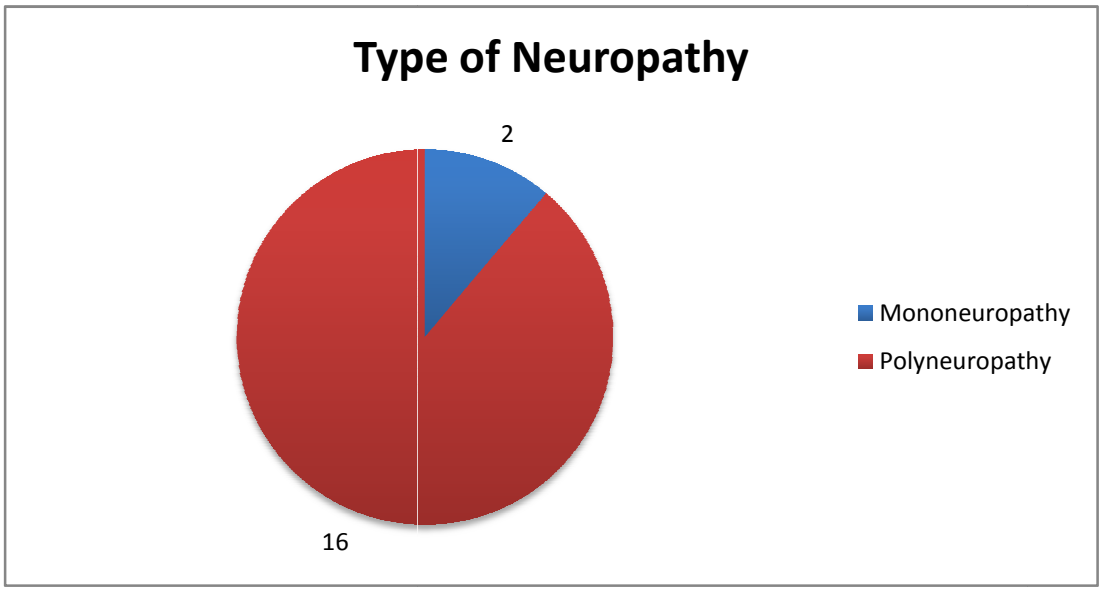
S NCV (m/s)

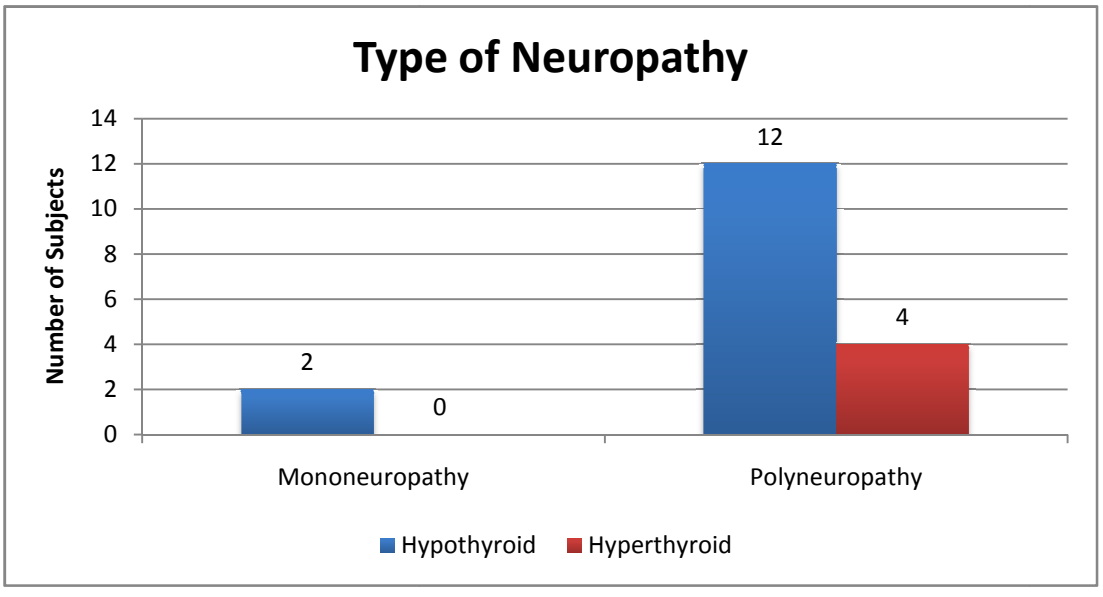

S NCV (m/s)
Man Values
80.00
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
51.80
57.17
52.85
60.55
67.24
62.09
58.42
54.58
63.13
58.72
65.96
58.46
Right Median
Left Median
Right Ulnar
Left Ulnar
Right Sural
Left Sural
Hypothyroid
Hyperthyroid

S NCV (m/s)		Right Median	Left Median	Right Ulnar	Left Ulnar	Right Sural	Left Sural
All	N	50	50	50	50	50	50
	Mean	53.20	54.85	65.90	57.42	61.99	64.01
	SD	8.91	8.56	56.80	7.39	12.81	13.77
Hypothyroid	N	37	37	37	37	37	37
	Mean	51.80	52.85	67.24	58.42	63.13	65.96
	SD	8.99	7.97	65.75	8.04	13.66	12.97
Hyperthyroid	N	13	13	13	13	13	13
	Mean	57.17	60.55	62.09	54.58	58.72	58.46
	SD	7.65	7.81	13.48	4.11	9.70	15.01
P value Unpaired t Test		0.1482	0.2262	0.6547	0.3334	0.2172	0.1256

By conventional criteria the association between the study groups and S NCV distribution is considered to be not statistically significant since $p > 0.05$

TYPE OF NEUROPATHY

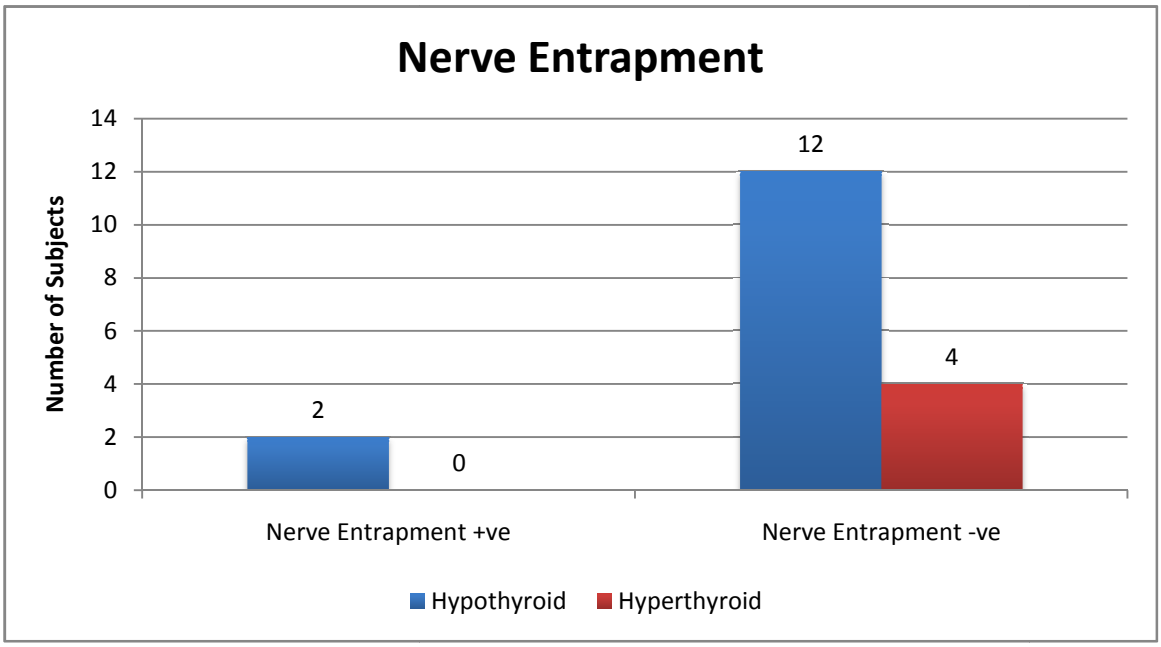




Type of Neuropathy	All	%	Hypothyroid	%	Hyperthyroid	%
Mononeuropathy	2	4.00	2	5.41	0	0.00
Polyneuropathy	16	32.00	12	32.43	4	30.77
Total	18	36	14	38	4	31
P value Fishers Exact Test			0.9999			

By conventional criteria the association between the study groups and type of neuropathy is considered to be not statistically significant since $p > 0.05$

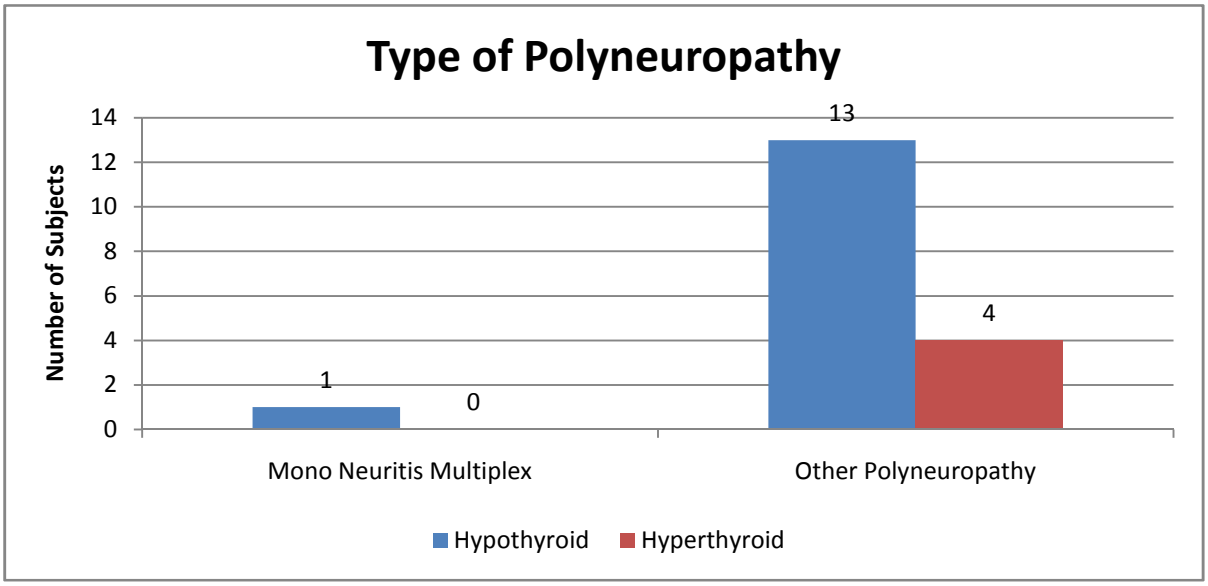
NERVE ENTRAPMENT



Nerve Entrapment	All	%	Hypothyroid	%	Hyperthyroid	%
Nerve Entrapment +ve	2	11.11	2	14.29	0	0.00
Nerve Entrapment -ve	16	88.89	12	85.71	4	100.00
Total	18	100	14	100	4	100
P value Fishers Exact Test			0.9999			

By conventional criteria the association between the study groups and nerve entrapment is considered to be not statistically significant since $p > 0.05$

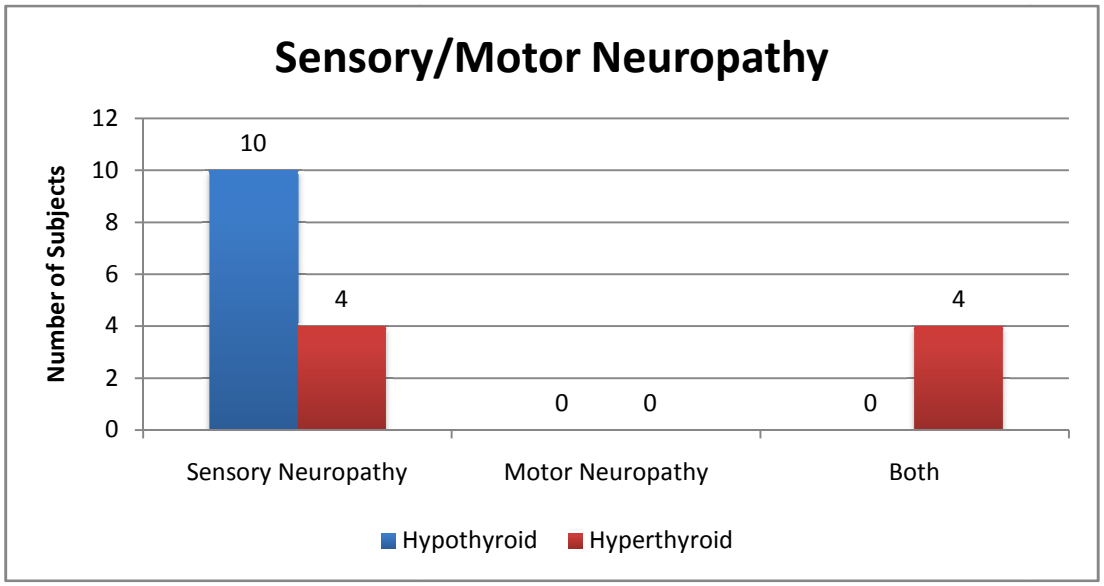
TYPE OF POLYNEUROPATHY



Type of Polyneuropathy	All	%	Hypothyroid	%	Hyperthyroid	%
Mono Neuritis Multiplex	1	11.11	1	100.00	0	76.47
Other Polyneuropathy	17	88.89	13	0.00	4	23.53
Total	18	100	1	100	17	100
P value Fishers Exact Test			0.9999			

By conventional criteria the association between the study groups and type of polyneuropathy is considered to be not statistically significant since $p > 0.05$

Sensory/Motor Neuropathy



Sensory/Motor Neuropathy	All	%	Hypothyroid	%	Hyperthyroid	%
Sensory Neuropathy	14	77.78	10	100.00	4	50.00
Motor Neuropathy	0	0.00	0	0.00	0	0.00
Both	4	22.22	0	0.00	4	50.00
Total	18	100	10	100	8	100
P value Fishers Exact Test			0.0229			

Results

In patients belonging to hypothyroid group, the majority had sensory neuropathy (n=10, 100%). In hyperthyroid group, the majority had sensory neuropathy (n=4, 50%). The increased incidence of sensory neuropathy in hypothyroid group compared to hyperthyroid group is statistically significant as the p value is 0.0229 as per fishers exact test indicating a true difference among study groups.

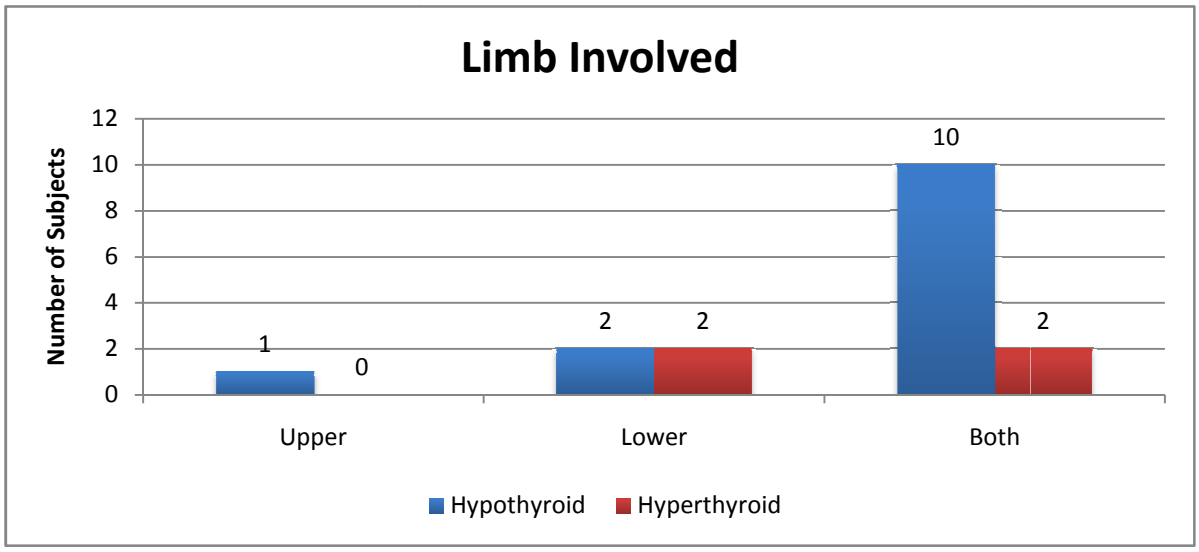
Discussion

The incidence of sensory neuropathy was meaningfully more in hypothyroid group compared to hyperthyroid group by 50.00 percentage points. This significant difference of 2 times increase in incidence of sensory neuropathy in hypothyroid group compared to hyperthyroid group is true and has not occurred by chance.

Conclusion

In this study we can safely conclude that incidence of sensory neuropathy was significantly and consistently higher in hypothyroid group compared to hyperthyroid group.

LIMB INVOLVED



Limb Involved	All	%	Hypothyroid	%	Hyperthyroid	%
Upper	1	5.88	1	7.69	0	0.00
Lower	4	23.53	2	15.38	2	50.00
Both	13	70.59	11	76.92	2	50.00
Total	18	100	13	100	4	100
P value Fishers Exact Test			0.3295			

By conventional criteria the association between the study groups and limb involvement is considered to be not statistically significant since $p > 0.05$

RESULTS:

Following are the results from our study

1. Majority of the hypothyroid Group patients belonged to the 31-40 years age class interval (n=13, 35.14%) with a mean age of 35.37 years. In the hyperthyroid group patients, majority belonged to the ≤ 30 years age class interval (n=6, 46.15%) with a mean age of 34.77 years.

2. Majority of the hypothyroid Group patients belonged to female gender, class interval (n=28, 75.68). In the hyperthyroid group patients, majority belonged to the female gender class interval (n=7, 53.85%)

3. Majority of the hypothyroid Group patients belonged to the 7-12 months duration of symptoms class interval (n=14, 37.84). In the hyperthyroid group patients, majority belonged to the 4-6 months duration of symptoms class interval (n=7, 53.85%)

4. In patients belonging to hypothyroid Group, the mean CMAP- median is 14.74 mv, CMAP – ulnar is 10.23 mv, CMAP – peroneal is 6.82 mv and CMAP – tibial is 14.33 mv. Similarly in hyperthyroid patients CMAP- median is 13.50 mv, CMAP – ulnar is 10.44 mv, CMAP – peroneal is 5.90 mv and CMAP – tibial is 13.92 mv. . The increased mean CMAP measurements overall and in hypothyroid

group compared to the hyperthyroid Group is statistically significant as the p value is < 0.05 as per unpaired t- test indicating a true difference among study groups.

5. In patients belonging to hypothyroid Group, the mean SNAP- median is 39.31uv, SNAP – ulnar is 29.65uv and SNAP – suralis 10.73uv. Similarly in hyperthyroid patients SNAP - median is 43.74 uv., SNAP – ulnar is 31.55 uv. and SNAP – sural is 12.54 uv.. . The increased mean SNAP measurements overall and decreased in hypothyroid group compared to the hyperthyroid Group is statistically significant as the p value is < 0.05 as per unpaired t- test indicating a true difference among study groups.

6. By conventional criteria the association between the study groups and various parameters like M distal latency, M ncv, F wave, S distal latency, S ncv, are considered to be not statistically significant since p > 0.05

DISCUSSION:

1. Our study concludes that hypothyroid individuals are more prone for sensory motor axonal polyneuropathy.this was quoted by many authors also.
2. Duffy et al quotes 19% of hyperthyroid individuals had sensory axonal neuropathy which matches our study that 30.7% of hyperthyroid individuals had it.
3. Our study didn't show any F wave changes in median and peroneal nerves this is in contrary to udhayakumar et al.
4. O malley et al and our study was similar in showing sensory threshold abnormalities in multiple nerves.
5. Schutt et al clearly demonstrated motor conduction abnormalities whereas our contradicts it by having predominant sensory conduction abnormalities.

According to khedr EM et al 5-92% of individuals had carpal tunnel syndrome.in our study 15% of individuals had it.

CONCLUSION

- Out of 50 patients 18 patients have neuropathy.14 of them were hypothyroid and 4 of them were hyperthyroid individuals.so it is observed that predominantly hypothyroid individuals are predisposed to develop neuropathy.
- 2 patients had mononeuropathy and 16 of them had polyneuropathy.
- Entrapment features like carpal tunnel syndrome was present in 2 individuals. both the patients were hypothyroid.
- 1 patient had features of mononeuritis multiplex.
- 14 patients had predominantly sensory neuropathy and 4 individuals had both sensory and motor polyneuropathy.
- 13 patients had both upperlimb and lowerlimb involvement.
- 4 patients had predominantly lower limb involvement and 1 patient had predominantly upper limb involvement.
- The amplitude of CMAP and SNAP were particularly altered in both group and it was also statistically significant.Thereby it reflects the axonal pattern of sensory loss,which is expceted in thyroid illness.
- The following were the most common neurological abnormalities deteted.
    - sensory axonal poly neuropathy,
    - mononeuropathy involving the sural nerve,
    - mononeuritis multiplex pattern,

- entrapment like capal tunnel involving median nerve.

- In a nutshell hypothyroid patients are more prone to develop neuropathy predominantly involving the sensory nerves in both lower limbs.
- Electrophysiological studies can be useful in the diagnosis of subclinical polyneuropathy.
- Our study clearly depicts that peripheral neurological involvement is more prevalent in newly detected thyroid dysfunction.
- So that nerve conduction studies(electrophysiological study) can be included in the early part of diagnostic work up panel in newly deteted thyroid illness.
- Since this neuropathy at early stage is reversible, it can also be used to test the prognosis of hypothyroidism and hyperthyroidism on Standard treatment.

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PROFORMA

Name:

Age: 1) 20-30 2) 30-40 3)40- 50 4) 50- 60yrs Sex: 1.M 2.F

Locality: Contact No:

Complaints:

Past history:

Condition	Yes	No	If yes specify
Diabetes			
Renal failure			
Autoimmune disease			
Liver failure			
Connective tissue disorder			
H/o chronic drug Intake			
H/o of recent fever			

Personal H/O:

Food : 1.Veg 2.Non Veg

Smoking: 1. Yes 2. No

Alcohol Intake: 1. Yes 2. No

Vitals-

BP: PR: RR: Temperature:

Systemic Examination-

CVS: RS: P/A:

CNS:

Investigations

CBC :

RFT :

RBS :

Thyroid Function Test

TSH	Free T3	Free T4

Nerve Conduction Study

Comment:

GOVT. STANLEY MEDICAL COLLEGE, CHENNAI – 600001

INFORMED CONSENT

A STUDY ON NERVE CONDUCTION ABNORMALITIES IN PATIENTS WITH NEWLY DETECTED THYROID DYSFUNCTION AT GOVERNMENT STANLEY MEDICAL COLLEGE HOSPITAL, CHENNAI.

Place of study: Govt. Stanley medical college, Chennai

I ……. have been informed about the details of the study in my own language.

I have completely understood the details of the study.

I am aware of the possible risks and benefits, while taking part in the study. I agree to collect samples of blood/saliva/urine/tissue if study needs.

I understand that I can withdraw from the study at any point of time and even then, I can receive the medical treatment as usual.

I understand that I will not get any money for taking part in the study.

I will not object if the results of this study are getting published in any medical journal, provided my personal identity is not revealed.

I know what I am supposed to do by taking part in this study and I assure that I would extend my full cooperation for this study.

Volunteer:	Witness:
Name and address	Name and address
Signature/thumb impression:	Signature/thumb impression
Date:	Date:
Investigator Signature and date	

தைராய்டு செயலிழப்பு நோயாளிகளின் நரம்புகடத்துதல் திசைவேகம் பற்றிய ஒரு ஆய்வு

ஆய்வாளர் :

மரு. ப. அருண்காந்தி முதுநிலை பட்ட மேற்படிப்பு மாணவர் பொது மருத்துவ பட்டபடிப்பு
அரசு ஸ்டான்லி மருத்துவமனை

பங்கேற்பாளரின் தகவல் படிவம்

நீங்கள் இந்த ஆய்வில் பங்கேற்க அழைக்கப்படுகிறீர்கள். இந்த ஆய்வில் பங்கேற்கும்முன், இதன் நோக்கத்தையும், முறைகளையும், இதனால் ஏற்படும் பின்விளைவுகளையும் நீங்கள் அறிந்து கொள்ள ஆய்வாளர் அளிக்கும் தகவல்:

உங்கள் நோயின் வரலாறும், உங்களின் முழு உடல் பரிசோதனையும் தெளிவாகவும் விரிவாகவும் பதிவு செய்யப்படும். இந்த ஆய்வின் முடிவுகள் மருத்துவக் காரணங்களுக்காகவும், மருத்துவ கல்விக்காகவும் பயன்படுத்தப்படும். இந்த ஆய்வு பற்றிய சந்தேகங்களுக்கு உரிய முறையில் விளக்கம் அளிக்கப்படும். தங்களைப்பற்றிய தகவல்கள் இரகசியமாக பாதுகாக்கப்படும். இந்த ஆய்வில் இருந்து எப்போது வேண்டுமானாலும் தாங்கள் எவ்வித முன்னறிவிப்பின்றியும், எவ்வித சட்ட சிக்கலும் இன்றி விலகிக்கொள்ளலாம்.

இந்த ஆய்வில் பங்கேற்குமாறு தங்களை கட்டுகொள்கிறேன்

நன்றி

ஆய்வாளர் கையொப்பம் நோயாளியின் கையொப்பம்

(மரு. ப. அருண்காந்தி)

தைராய்டு செயலிழப்பு நோயாளிகளின் நரம்புகடத்துதல் திசைவேகம் பற்றிய ஒரு ஆய்வு

சுயஒப்புதல் படிவம்

நான் இந்த ஆராய்ச்சியில் விவரங்களை முற்றிலும் புரிந்து கொண்டேன். ஆய்வில் பங்கு எடுத்து போது, சாத்தியமான அபாயங்கள் மற்றும் பயன்களைபற்றி நான்அறிந்துள்ளேன். நான் எந்தவொருவேளையிலும் ஆய்வில் இருந்து திரும்பமுடியும், அதன் பின்னர் நான்வழக்கம் போல் மருத்துவ சிகிச்சை பெற முடியும் என்று புரிந்துகொள்கிறேன். நான் ஆய்வில் பங்கு எடுத்து பணம் எதையும் பெறமுடியாது என்று அறிந்துள்ளேன்.

இந்த ஆய்வின் முடிவுகள் எந்த மெடிக்கல் ஜர்னலில் வெளியிடப்பட இருந்தால் நான் எதிர்க்கவில்லை, என் தனிப்பட்ட அடையாளத்தை வெளிப்படுத்தப்பட்டு இருக்ககூடாது. நான் இந்த ஆய்வில்பங்கெடுப்பதன் மூலம் நான் என்ன செய்யபோகிறேன் என்று தெரியும். நான் இந்த ஆய்வில் என் முழு ஒத்துழைப்பையும் கொடுப்பேன் என்று உறுதியளிக்கிறேன்.

தன்னார்வளர்	சாட்சி
பெயர்மற்றும்முகவரி	பெயர்மற்றும்முகவரி
கையொப்பம் / விரல்ரேகை:	கையொப்பம் / விரல்ரேகை:

ஆராய்ச்சியாளர்

கையொப்பம்மற்றும்தேதி

INSTITUTIONAL ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work	: A Study on Nerve conductor abnormalities in patients with Newly Detected Thyroid Dysfunction.
Principal Investigator	: Dr. Arun Gandhi P
Designation	: PG MD (General Medicine)
Department	: Department of General Medicine Government Stanley Medical College, Chennai-01

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 11.02.2015 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institutions).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY,
IEC, SMC, CHENNAI

MEMBER SECRETARY
ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE
CHENNAI-600 001.

KEY TO MASTER CHART

SEX

Male- 1

Female-2

THYROID STATUS

Hypothyroidism-1

Hyperthyroidism-2

DURATION OF THYROID SYMPTOMS

less than 3 months -1

3 -6 months -2

6mo-1 yr duration -3

greater than 1 yr duration -4

TYPE OF NEUROPATHY

mononeuropathy -1

polyneuropathy -2

none -3

ENTRAPMENT NEUROPATHY

Present -1

Absent -2

None -3

TYPE OF POLYNEUROPATHY

Mononeuritis Multiplex -1

Others -2

None -3

CLASSIFICATION OF NEUROPATHY

Sensory neuropathy -1

Motor neuropathy – 2

Both -3

None -4

LIMB INVOLVEMENT

Upper limb only -1

Lower limb only -2

Both limbs -3

None -4

S.NO	NAME	AGE	SEX	THYROID STATUS	DURATION OF THYROID SYMPTOMS	TSH	FREE T4	FREE T3	type of neuropathy (mono or poly)	entrapment present or not	type of polyneuropathy (mononeuritis multiplex or others	sensory or motor neuropathy or both	upperlimb or lowerlimb or both involvemrnt	INFERENCE
1	SUMATHY	33	2	1	3	40	0.4	1	3	3	3	4	4	
2	JAYANTHY	37	2	1	2	35	0.6	1.4	2	2	2	1	3	SENSORY AXONAL POLYNEUROPATHY IN BOTH UPPER AND LOWER LIMBS MORE IN LOWER LIMB
3	JAHITHA	47	2	1	3	18	0.4	2.5	2	1	2	3	3	SENSORY POLYNEUROPATHY IN BOTH LOWER LIMBS INVOLVING SURAL NERVE AND CARPEL TUNNEL SYNDROME IN BOTH UPPER LIMB
4	DIVYA	22	2	1	1	11.2	0.92	1.1	3	3	3	4	4	
5	NIRMALA	32	2	1	3	18.6	0.46	2.3	1	2	2	1	2	RIGHT SURAL AXONAL NEUROPATHY
6	CHITRA	25	2	1	3	48.8	0.7	2.2	3	3	3	4	4	
7	DEVI	25	2	1	2	12.94	0.87	1.92	3	3	3	4	4	
8	ILAVARASI	28	2	1	2	20.9	0.4	2	3	3	3	4	4	
9	LAKSHMI	42	2	1	2	29.3	0.8	2.6	2	2	2	1	3	SENSORY AXONAL POLYNEUROPATHY IN BOTH UPPER AND LOWER LIMBS
10	THULASI	21	2	1	4	40	0.4	1.9	2	2	2	1	1	SENSORY AXONAL POLYNEUROPATHY IN UPPER LIMB
11	SIVAGAMI	42	2	1	2	9.5	0.33	2	2	2	2	1	3	SENSORY AXONAL POLYNEUROPATHY IN BOTH UPPER AND LOWER LIMBS MORE SEVERE IN LOWER LIMB
12	HEMALATHA	48	2	1	3	11.2	0.6	1.4	2	2	2	1	3	RIGHT MEDIAN AND RIGHT SURAL SENSORY AXONAL NEUROPATHY
13	KAMATCHI	37	2	1	3	8.9	0.8	1.9	3	3	3	4	4	
14	SHANTHI	36	2	1	3	7.6	0.9	2.1	2	2	1	3	3	SENSORY MONO NEURITIS MULTIPLEX INVOLVING SENSORY AXONS IN LOWER LIMB AND IN RIGHT ULNAR NERVE
15	MAGESH	24	1	1	4	150	0.2	1.3	3	3	3	4	4	
16	RADHA	42	2	1	3	6.5	0.7	2.8	3	3	3	4	4	
17	HEMALATHA	21	2	2	2	0.07	10.5	14.2	3	3	3	4	4	
18	SUMATHY	27	2	2	3	0.074	3.46	9.87	2	2	2	1	2	SENSORY AXONAL NEUROPATHY INVOLVING BOTH SURAL

														NERVE
19	RAVI	42	1	2	2	0.056	12	15.6	2	2	2	1	3	SENSORY AXONAL POLYNEUROPATHY IN BOTH UPPER AND LOWER LIMBS
20	AMALA	26	2	1	2	6.9	0.4	1.4	3	3	3	4	4	
21	GOWSMOAIDEEN	50	1	2	4	0.45	12	19	3	3	3	4	4	
22	GOMATHY	33	2	1	3	40	0.4	2	3	3	3	4	4	
23	PARVATHY	37	2	1	4	20.2	0.35	1.1	2	2	2	1	3	SENSORY AXONAL POLYNEUROPATHY IN BOTH UPPER AND LOWER LIMBS MORE IN LOWER LIMB
24	JUBEETHA	47	2	1	3	33	0.8	1.9	2	1	2	3	3	SENSORY POLYNEUROPATHY IN BOTH LOWER LIMBS INVOLVING SURAL NERVE AND CARPEL TUNNEL SYNDROME IN BOTH UPPER LIMB
25	DIVYA	22	2	1	2	18.6	0.7	1.47	3	3	3	4	4	
26	RANI	28	2	1	1	11.9	0.22	1.59	1	2	2	1	2	RIGHT SURAL AXONAL NEUROPATHY
27	RANJANI	27	2	2	2	0.09	9.8	12	3	3	3	4	4	
28	ARCHANA	26	2	1	1	18	0.8	2	3	3	3	4	4	
29	PACHAIAMMAL	42	2	1	4	21	0.4	1.45	3	3	3	4	4	
30	VIKRAM	31	2	1	3	21	0.6	1.9	2	2	2	1	3	SENSORY AXONAL POLYNEUROPATHY IN BOTH UPPER AND LOWER LIMBS
31	RUKMANI	37	2	1	3	48.8	0.7	2.2	2	2	2	1	3	SENSORY AXONAL POLYNEUROPATHY IN BOTH UPPER AND LOWER LIMBS MORE SEVERE IN LOWER LIMB
32	VANITHA	35	2	1	2	21.2	0.87	2.5	2	2	2	3	3	RIGHT MEDIAN AND RIGHT SURAL SENSORY AXONAL NEUROPATHY
33	SRIDEVI	47	2	1	3	15	0.5	1.88	3	3	3	4	4	
34	MANIKANDAN	38	1	1	4	33	0.7	1.9	3	3	3	4	4	
35	PANDIYAN	56	1	1	2	96	0.4	1.2	3	3	3	4	4	
36	RAJU	42	1	1	4	6.5	0.7	2.8	3	3	3	4	4	
37	LATHA	21	2	2	1	0.56	19.9	18.4	3	3	3	4	4	
38	VIJAY	42	1	2	2	0.049	4	8.6	2	2	2	1	2	SENSORY AXONAL NEUROPATHY INVOLVING BOTH SURAL NERVE
39	JANAKI	28	2	2	4	0.08	11.8	18.2	2	2	2	1	3	SENSORY AXONAL POLYNEUROPATHY IN BOTH UPPER AND LOWER LIMBS
40	BARANI	43	2	1	1	13.1	0.82	1.22	3	3	3	4	4	

41	RAHMAN	39	1	2	2	0.77	16	15.3	3	3	3	4	4	
42	BALAN	52	1	1	3	7.9	0.98	1.67	3	3	3	4	4	
43	MARY	37	1	2	2	9.9	1	2.3	3	3	3	4	4	
44	SUBHASHINI	23	2	2	2	0.022	21	33	3	3	3	4	4	
45	PARTHIBAN	24	1	1	1	9.8	1	2.5	3	3	3	4	4	
46	CHELLAMMAL	50	2	2	4	0.4	15	17.8	3	3	3	4	4	
47	RAMASAMY	33	1	1	4	45	0.7	2.7	3	3	3	4	4	
48	ADIMOOLAM	45	1	2	4	0.3	10.1	16.7	3	3	3	4	4	
49	ILAYAVENDAN	28	1	1	2	20.9	0.4	2.1	3	3	3	4	4	
50	MURALI	37	1	1	2	8.9	0.8	1.8	3	3	3	4	4	